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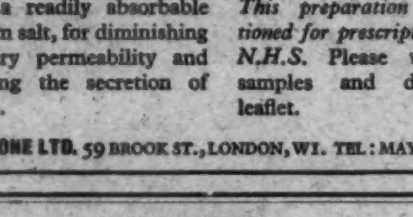

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 21 1952

STRUCTURAL AND FUNCTIONAL ADAPTATION IN RENAL FAILURE*

BY

ROBERT PLATT, M.D., M.Sc., F.R.C.P.
Professor of Medicine, University of Manchester

[WITH SPECIAL PLATE]

I am very conscious of the honour, and the responsibility, of being asked to take part in a series of lectures which began in 1581 during the reign of another Queen Elizabeth, a series in which William Harvey himself participated. Richard Bright gave these lectures in 1837, but unfortunately they do not seem to have been published, and we are ignorant even of his title, though we may make a shrewd guess as to his subject. Reginald Southey chose Bright's disease for his discourse in 1881, and Rose Bradford was Lumleian Lecturer in 1920, but did not choose to speak on renal disease—which, as I think, is a pity; for some of his original work on the kidney is still of such importance that I shall in due course quote from it, more than half a century after its publication. Croonian Lecturers of this College also, from time to time, have chosen the kidney as their theme.

Adaptive Processes

My own title is "Structural and Functional Adaptation in Chronic Renal Failure," and I shall reserve the right to interpret very freely my self-imposed terms of reference. The study of human disease reveals frequent evidence of the wonderful adaptations which take place in the body in response to pathological situations. A good example is the increased cardiac output which regularly occurs in chronic anaemia (Sharpey-Schafer, 1944). Its purpose is surely to maintain an adequate oxygen supply in spite of a greatly diminished oxygen-carrying power. Sometimes these adaptive processes seem to be a consequence of extreme conditions acting on already existing and well-recognized physiological mechanisms; for instance, the hyperpnoea of acidosis. Perhaps they are really all of this nature. Sometimes it appears to be no more than a lucky accident that the disorder sets in motion a process tending towards its own neutralization. Sometimes the adaptation seems to be specially developed to meet an existing situation.

The raised blood urea in renal disease is a simple example of an adaptation. Urea is excreted by glomerular filtration, and therefore must increase in the blood as destruction of renal tissue leads to diminution of filtration rate. As it does so it automatically reaches a point where the increased height of the blood urea ensures its own excretion. Suppose that you have two funnels—a large and a small one. The large one filters at the rate of 100 ml. per minute and is filtering a solution of urea containing 30 mg. per 100 ml. Obviously 30 mg. of urea per minute appears in the filtrate. The smaller funnel filters at only 30 ml. per minute, but contains a stronger solution of urea—namely, 100 mg. per 100 ml. Obviously 30 mg. of urea per minute is filtered also by this funnel. You may look upon this as a greatly over-simplified example of what happens in renal failure, the larger funnel representing the normal kidney and the smaller funnel the kidney of chronic renal disease filtering a solution of much higher urea content.

I shall return later to the question of urea excretion in more detail, but I have chosen it as a very simple and self-evident example of an adaptation; so simple, in fact, that we may doubt the justification of calling it an adaptation at all. It may be purely fortuitous that urea retention leads to more efficient urea excretion. But in the more complicated adaptive processes of the body—for instance, the increased cardiac output of anaemia to which I have already referred—it is difficult to doubt that there is a purpose in the phenomenon. If we recognize a purpose then we are speaking teleologically, and that is still thought to be a sin by many physiologists and biologists, so I would like to say a word or two about it. Teleology is explanation by reference to the realization of some purpose or end, contrasted with explanation by efficient causes only. Now adaptation, in our present sense of the term, is making something suitable to or for a purpose (I have consulted recognized authorities for my definitions). Thus it is quite impossible to consider phenomena as adaptive in nature without admitting that they have purpose, and impossible to discuss their purpose without resorting to teleology.

In many of the body's adaptive processes (unlike the simple example of the blood urea) we may see the purpose before knowing or discovering the mechanism by which it is mediated or even the stimulus which sets it in motion, and here the process of teleological thinking, if not misused, can be a valuable aid to hypothesis.

The weakness of teleology is that it never takes us beyond the stage of hypothesis, and as Sir Thomas Lewis (1925) said: "Hypothesis has its right place—it forms a working basis; but it is an acknowledged makeshift, and as a final expression of opinion it is an open confession either of failure or at best of purpose unaccomplished." I fear that these lectures will contain several examples of purpose unaccomplished.

*The first of two Lumleian Lectures delivered before the Royal College of Physicians of London on April 1 and 3, 1952.

Before going further I had better define renal failure, for it is entirely of renal failure that I shall be speaking. It is the function of the kidney to preserve the composition of the extracellular fluid, and when the kidney fails in that function disturbances in the chemical structure of the body fluid occur. The most ready evidence of renal failure is the increase in the urea content of the blood or plasma, so the term uraemia is equally appropriate, though less satisfactory, for it concentrates attention on but one not very important aspect of the subject. Functional tests may detect a state of renal insufficiency before renal failure has actually occurred. I shall not deal with the oedematous syndromes of renal disease or with the acute renal failure which occurs in tubular necrosis and sometimes in acute nephritis, nor shall I discuss the extrarenal causes of uraemia unless these are referred to for purposes of argument or illustration.

Chronic renal failure has many causes, the commonest of which are nephritis in its terminal stage, chronic pyelonephritis, and the malignant phase of essential hypertension (Platt and Davson, 1950). Their common structural basis is a diminution in the number of functioning nephrons.

Structural Adaptation

The most obvious adaptive or compensatory process in renal disease is a structural one. It is well known that in cases of unilateral renal disease in man the sound kidney becomes hypertrophied, and functional studies after nephrectomy have frequently shown that the renal blood flow and glomerular filtration rate of the remaining kidney may reach about 80% of that of the two normal organs (Weiss and Chasis, 1943; Welsh, Wellen, Taylor, and Rosenthal, 1944; Hogeman, 1948).

In animals, unilateral nephrectomy generally results in hypertrophy of the remaining kidney to about 75% of the original weight of the two kidneys (Addis, 1948).

Renal hypertrophy after unilateral nephrectomy seems to be dependent upon the integrity of the anterior pituitary and probably upon its growth hormone, for it does not take place in hypophysectomized animals (Winternitz and Waters, 1940; White, Heinbecker, and Rolf, 1941), whereas the administration of anterior-lobe extract causes renal hypertrophy even in castrated animals (Selye, Stone, Nielsen, and Leblond, 1945) where the action of pituitary gonadotrophic hormone on testosterone production can be excluded.

Renal hypertrophy can be produced in young animals by a high-protein diet (Addis, MacKay, and MacKay, 1926), but not to the same extent by the administration of urea (MacKay, MacKay, and Addis, 1931; Baxter and Cotzias, 1949).

In experiments which Platt, Roscoe, and Smith (1952) have been making on rats, more than half of one kidney is removed at a first operation and the remaining whole kidney is removed about ten days later (Fig. A). The initial weight of the remaining renal remnant is calculated from the weight of kidney removed and the weight of kidney per unit of body weight in normal control rats. In 18 experiments the calculated gain in weight of the remaining piece of kidney varied considerably, but was over 100% in four cases, with a mean gain of 66%. This hypertrophy had taken place in about two to three weeks after the second operation. Fig. 1a (Special Plate) shows the normal histology of the rat kidney and Fig. 1b the histology of the remaining fragment. The striking change is one of tubular hypertrophy, most obvious in the proximal tubules and the loops of Henle, and this is due largely to cellular hyperplasia, mitoses being frequently observed. The tubular lumen is often dilated (Figs. 2a and 2b). The glomeruli are also enlarged and altered in shape.

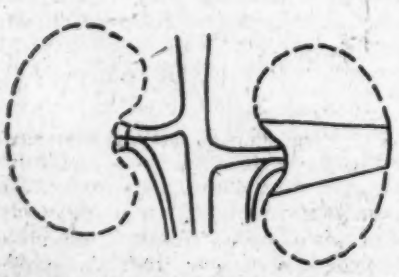
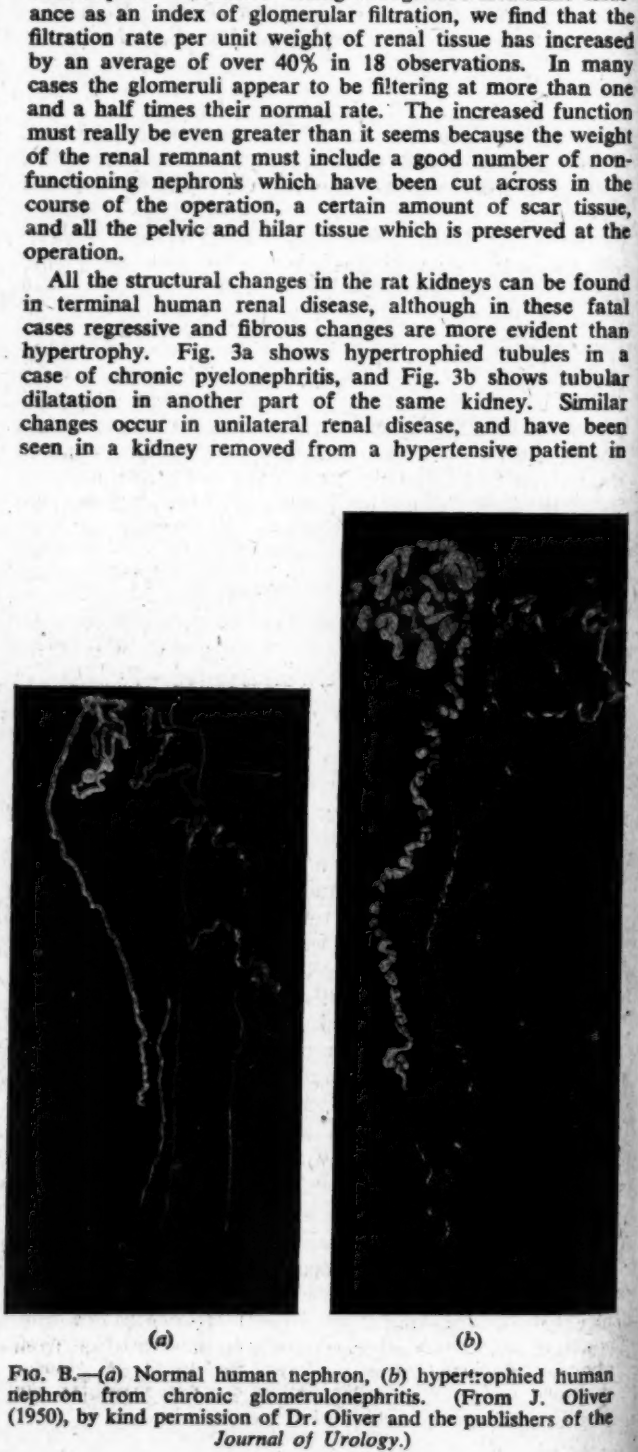


FIG. A.—Removal of renal tissue in experimental renal failure. Only a small portion of the left kidney remains.

In some parts of the kidney, however, especially where a replacement fibrosis of non-functioning tubules has taken place, the tubules are much dilated and show a low form of atypical epithelium. Often this seems to occur in tubules which have previously hypertrophied. I am indebted to Dr. Smith for the photomicrographs. Similar observations have of course been made by other workers (Addis, 1948). Not only do the nephrons enlarge but the work done by each nephron increases. Using endogenous creatinine clearance as an index of glomerular filtration, we find that the filtration rate per unit weight of renal tissue has increased by an average of over 40% in 18 observations. In many cases the glomeruli appear to be filtering at more than one and a half times their normal rate. The increased function must really be even greater than it seems because the weight of the renal remnant must include a good number of non-functioning nephrons which have been cut across in the course of the operation, a certain amount of scar tissue, and all the pelvic and hilar tissue which is preserved at the operation.

All the structural changes in the rat kidneys can be found in terminal human renal disease, although in these fatal cases regressive and fibrous changes are more evident than hypertrophy. Fig. 3a shows hypertrophied tubules in a case of chronic pyelonephritis, and Fig. 3b shows tubular dilatation in another part of the same kidney. Similar changes occur in unilateral renal disease, and have been seen in a kidney removed from a hypertensive patient in



(*a*) (*b*)

FIG. B.—(*a*) Normal human nephron, (*b*) hypertrophied human nephron from chronic glomerulonephritis. (From J. Oliver (1950), by kind permission of Dr. Oliver and the publishers of the *Journal of Urology*.)

whom the abnormal kidney did not visibly excrete diodrast although the opposite kidney was functioning well in this respect.

These appearances of chronic renal disease would strongly suggest that, whereas most of the renal tissue may be destroyed, the functioning remnant is hypertrophied and may be working at an increased rate.

The beautiful morphological studies of Jean Oliver (1950), in which whole nephrons are separated by microdissection, have shown that the hypertrophy and hyperplasia in nephrons from human chronic renal disease occur chiefly in the glomerulus and proximal tubule, which latter is increased both in thickness and in length and to such an extent that its volume may be 20 times that of a normal proximal tubule. I have Dr. Oliver's permission to reproduce Fig. B from one of his papers. Oliver also shows that, while some tubules undergo this hyperplasia, others, as we have seen, are atrophied. Some show the peculiar anomaly of a hypertrophied tubule unattached to a glomerulus.

That the hyperplastic tubules actually have increased function Oliver (1944–5 and 1950) has also shown by the intravital injection of trypan blue in dogs suffering from chronic canine Bright's disease. The nephrons absorb and store the dye in a normal manner but in greatly increased amount.

I shall several times refer back to these studies of structure in chronic renal disease when considering renal function, for it is most important that functional studies should take them into account, and I would emphasize particularly the contrast between a low glomerular filtration rate due to conditions imposed upon a kidney of normal size, as in heart failure, and a low glomerular filtration rate due to loss of nephrons. In the first instance the rate of filtration per glomerulus is low, and in the second instance, as in our rats, it is high. The total effective renal function is reduced owing to loss of tissue, but the work of each remaining unit is increased. Workers in the field of applied renal physiology have frequently overlooked this essential distinction, and at the risk of overemphasis I will illustrate it by a simile from industry. The total production or output of a factory may fall for one of two reasons. The team of workers may become slack or may not have enough to do, like the nephrons in heart failure; or the team may have been seriously depleted in numbers owing to illness, the few remaining workers actually putting in overtime in an unsuccessful attempt to compensate for the absence of their fellows. The latter is the state of affairs in experimental renal failure, as our obliging rats have clearly demonstrated, and there is good reason to believe that it is the state of affairs also in chronic renal failure in the human subject. If we only study the total production of the factory, without regard to the output per man, or in the case of the kidney the overall function without regard to structure, we fail to distinguish between these two causes of inadequacy, and, since the behaviour of the tubule cells is in a large measure dependent upon the rate at which glomerular filtrate is reaching them, the distinction is of primary importance in the interpretation of the phenomena of renal disease.

Functional Adaptation: Isosthenuria

One of the constant signs of renal failure is the inability of the kidney to produce a concentrated urine, and it is well known that the specific gravity of the urine becomes relatively fixed at about 1010, which is approximately that of the blood plasma minus its proteins. Studies of osmotic pressure or "osmolarity" as determined by the freezing-point of the urine again show a similarity to the osmolarity of blood plasma. Osmolarity depends upon the number of molecules and ions in solution, whereas specific gravity depends upon their weight. Osmolarity is really the relevant factor in the present discussion, but, so long as the urine contains only its normal constituents and is free from abnormally heavy molecules such as those of glucose, diodrast, or inulin, specific gravity and freezing-point will give approximately equivalent information.

The phenomenon of isosthenuria—a urine of constant strength—was known to Koranyi as long ago as 1908 (see Volhard, 1931). It is still usually ascribed to tubular insufficiency—a concept which I presume means that the tubule cells are so damaged by disease that they are no longer able to perform the osmotic work required to provide a highly concentrated urine. That this supposition may be erroneous must be clear to anyone familiar with the experiments described by Rose Bradford in 1899, in which he showed that dogs, after removal of three-quarters of their renal tissue, also showed loss of concentrating power. His actual words are as follows: "The fragment of kidney left is quite able to excrete amounts of urea far larger than those usually excreted, as shown by giving the animals considerable quantities of an exclusively meat diet. A concentrated urine, however, is not passed, the increased output of urea being effected by an enormous increase in the amount of the urine." Obviously the remaining renal tubules of these animals have not been subject to any disease process likely to interfere with their ability to produce a hypertonic urine.

In 1939 Hayman *et al.* repeated these experiments and confirmed that after the removal of renal tissue in dogs loss of concentrating power occurred; and they made the further interesting observation that the urinary specific gravity could be increased again by artificially raising the plasma colloids or by reducing the blood pressure, procedures which would, of course, lower the glomerular filtration rate. Other observers, including ourselves, have shown that loss of renal tissue results in loss of concentrating power, and that this may occur independently of the development of hypertension—an observation which applies also to human renal failure, as any clinical observer of renal and hypertensive disease must know.

In a recent paper (1951) I have suggested that the loss of concentrating power is due to osmotic diuresis, and I would like now to examine this hypothesis somewhat more closely. When an osmotically active substance such as glucose or urea appears in the glomerular filtrate in excess it is excreted in dilute solution with a large quantity of water.

McCance (1945) showed, and Rapoport and his co-workers (1949a, 1949b) have since confirmed, that in normal subjects deprived of water the volume of urine passed can be enormously increased by producing an osmotic diuresis, and is in fact determined by the load of osmotically active substances requiring excretion. The interesting fact emerges that if a substance such as urea is ingested in considerable quantity in a state of dehydration the urine becomes *less* concentrated, not more, and in the fully developed state of osmotic diuresis the urine has an osmolarity which approaches or is equal to that of the plasma minus its proteins (Frey and Frey, 1950).

In order to put this to a personal test and to convince myself that a high blood urea reduced the urinary specific gravity, I have made some observations on myself. Under certain standard conditions the morning urine on seven occasions has had a specific gravity ranging from 1026 to 1032. If during the evening I ingest 30 g. of urea with the same amount of fluid as before, which means that I retire to bed with a blood urea of 80–90 mg. per 100 ml., the morning urine has a specific gravity of only 1016–1018. Thus it is quite clear that, in renal failure where the blood urea is high, the kidney must be acting continually under the conditions of an osmotic diuresis, and it is merely adapting itself in a physiological manner to this circumstance in producing a urine of low and fixed concentration.

The phenomenon of osmotic diuresis may be explained in one of two ways. There may be a limit to the amount of osmotic work which the tubule can perform, and to excrete urinary solutes in large quantity it is more economical of work to do so in dilute solution (Hervey, McCance, and Tayler, 1946; Rapoport, West, and Brodsky, 1949b). Homer Smith (1951), on the other hand, ascribes the diuresis to the fact that the excess of solutes interferes with the

reabsorption of water in the proximal tubule, and so the distal tubule is presented with more water than it can absorb.

Thus the isosthenuria of advanced renal failure is easily explained, and the nocturnal polyuria is no doubt also chiefly a consequence of the osmotic diuresis. But if the theory is to have universal application it must explain two further circumstances. The first is that diminution in concentrating power may occur in renal insufficiency before significant elevation of the plasma urea has taken place; and the second is that it may occur in the urine of the diseased kidney only, in cases of unilateral disease (Volhard, 1931; Platt, unpublished data), when the opposite kidney is quite capable of maintaining a normal plasma composition and no condition of osmotic diuresis would at first sight appear to exist.

Returning to the experiments of Rapoport and his co-workers, we remember that in the normal human subject deprived of water the volume of urine and its concentration depend upon the load of solutes requiring excretion. Now it is easy enough to speak in such terms of the intact kidney, but when we apply these findings to renal failure we must think in terms of nephrons rather than kidneys. From our experiments on rats we have seen that when renal substance is reduced the glomeruli enlarge and the infiltration rate per tubule (as estimated by creatinine clearance) is often increased by at least 50%. Thus the load of solutes entering each tubule per minute is greatly increased. Comparison of the structure of the remaining nephrons of the failing human kidney with those of the renal remnant in the rats strongly suggests that the same conditions hold, and, as I have already pointed out, a similar appearance is seen in the diseased kidney when only one organ of a pair is affected. Thus it would seem that in human renal failure the nephrons are acting under increased load even before the stage of nitrogen retention is reached, and should therefore behave as if conditions of osmotic diuresis obtained, producing a urine of low and fixed concentration.

There is another way of looking at this. When we come to discuss the excretion of urea and creatinine we shall see that, in spite of gross reduction of renal tissue in rats or in human disease, the rate of excretion of these substances remains virtually unaltered. There is thus no doubt at all that the solute load being excreted by each nephron is much increased, and this should lead to a condition in which the osmotic work required of each tubule is inconsistent with the production of a highly concentrated urine.

To sum up, then: in the physiological phenomenon known as osmotic diuresis the greater the load of osmotically active solutes requiring excretion the greater is the volume of the urine and the less does its concentration differ from that of plasma. In renal disease the solute load per nephron may be increased either by increasing the osmolarity of the filtrate (for example, by increasing the plasma urea concentration) or by increasing the filtration rate per nephron, or by both conditions acting together. It is maintained that only under such circumstances does isosthenuria occur and that it can therefore be explained as a physiological adaptation to an increased solute load.

I do not intend to dismiss altogether the possibility that damage to tubular cells plays a part. I merely point out that isosthenuria can occur under physiological conditions and in circumstances in which tubular damage is unlikely, and that most of the evidence points, as we shall see, to enhanced tubular activity in renal failure, as the structural appearances might lead us to predict. An exception is almost certainly to be found in acute tubular necrosis and in poisoning of the renal tubules by mercury, uranium, and oxalates. In these conditions (which are not discussed in these lectures) a true tubular failure probably occurs.

The Excretion of Urea and Creatinine

The amount of renal tissue removed from our rats was from 67 to 85%, more being removed in the later experiments than the earlier ones. In eight rats an average of 80% of their total renal tissue was removed. Before the operation their average creatinine output in 24 hours was 13 mg. After leaving time for recovery from the operation, their creatinine output in 24 hours was 13.3 mg., or 102% of what it had been before.

Compare this achievement of the rats with that of Mrs. B, who had renal failure due to chronic atrophic pyelonephritis. In March, 1947, her blood urea was 178 mg. per 100 ml. and her urea clearance only 9% of the average normal. The blood urea fluctuated a little from time to time, but the lowest figure we ever found was 140. In October, 1948, it was 176 mg. per 100 ml., almost identical with what it had been one year and seven months previously. Clearly she, though like the rats deprived of most of her functioning renal tissue, must have been excreting normal 24-hourly amounts of urea, otherwise her urea retention would have increased.

The most important single factor in securing this amazing adaptation is unquestionably that which I mentioned at the beginning of this lecture—namely, the effect of an increased plasma level of urea (or creatinine). If you filter a stronger solution of urea at a reduced rate the end-result may be the same in terms of urea excretion. The adjustment is, of course, automatic, for when the filtration rate is reduced the plasma urea (or creatinine) rises until its level ensures excretion at a rate corresponding with the rate of formation of urea or creatinine in the body. At that point, if the renal disease does not progress, the blood urea remains stationary. Incidentally, the same considerations answer the question, in case anyone should ask it, why the normal blood urea in the human subject is about 20 to 40 mg. per 100 ml. The reason is that that is the level necessary to ensure the excretion, at normal glomerular filtration rates, of an amount of urea equivalent to that which is being produced in the body by protein metabolism. If we had four kidneys instead of two our blood ureas would be only half as high.

It is interesting to calculate what would happen in a hypothetical case in which the normal urea clearance of 75 ml. per minute was suddenly reduced to 15 ml. per minute, or one-fifth of its former value. The blood urea would rise until it reached five times its normal level, or about 150 mg. instead of 30, after which it would rise no more. Assuming a total body fluid of 50 litres, and that 30 g. of urea is produced daily by protein metabolism the rate at which the blood urea would rise can be calculated and charted (Fig. C).* It will be seen that the blood urea would reach about 100 mg. in two days and nearly 130 mg. in four days. The calculation is not entirely academic in its importance, for it follows that if you have a patient in chronic uraemia whose urea clearance is 20% of normal and whose blood urea is 150 mg., and if by dialysis in some form of artificial kidney you reduced his blood urea to normal, it would rise again to 100 mg. in 48 hours. All this of course follows from a consideration of the clearance formula $\frac{UV}{P}$. This represents the amount of plasma being cleared of its urea (or creatinine) per minute. (The urea clearance is of course lower than the creatinine clearance because some urea is reabsorbed during its passage down

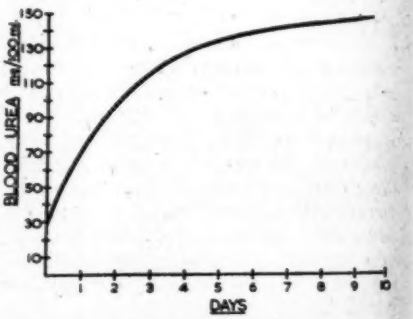


FIG. C.—Calculated rise of blood urea if urea clearance were suddenly reduced from 75 to 15 ml. a minute (see text).

*I am indebted to Mr. John Allen for the calculation and graph.

the tubule.) U is the concentration of urea (or creatinine) in the urine, P is the concentration in the plasma, and V is the volume of urine in millilitres per minute. UV thus represents the rate of urea excretion which, as we have seen, remains normal in quite advanced cases of renal failure, either natural or experimental. Now, if $\frac{UV}{P}$ is greatly diminished and UV remains normal, clearly P must be much increased, which is exactly what happens.

We have also seen that because of the osmotic diuresis V increases at the expense of U, and the fraction $\frac{U}{P}$, which is related to the osmotic work required to excrete urea or creatinine, is much reduced by a low value for U and a high value for P.

There are, however, three other adaptive processes possibly aiding the excretion of urea or creatinine. The first, which we have already considered, is the increased filtration rate per nephron. The second, which is probably of little significance, is that the slight nocturnal reduction in filtration rate which normally occurs does not take place in renal failure (Brod, 1949).* Thus excretion goes on by day and by night at the same rate. The third adaptation applies to the excretion of urea but not of creatinine. Creatinine is not reabsorbed nor actively excreted by the renal tubule, or not to any significant extent,† but urea is reabsorbed, or perhaps we should say it diffuses back into the plasma to the extent of about 30 to 60% at normal rates of urine flow. In other words, the normal urea clearance varies from 40 to 70% of the creatinine clearance. In renal failure reabsorption of urea in the renal tubules is reduced, so that the clearance of urea approaches that of creatinine or inulin (Chasis and Smith, 1938). This may at first sight appear to be an *ad hoc* adaptation or a lucky accident, but in fact it is again explicable as a natural result of an established physiological fact. Möller, McIntosh, and Van Slyke (1929) showed that urea clearance varied with urine flow, and Shannon (1938) has shown that in normal dogs the ratio of urea to creatinine excretion increases with the rate of urine flow, and the same phenomenon has been demonstrated less completely in man (Chasis and Smith, 1938). In chronic renal disease, although total urine flow may not be increased, the rate of flow per tubule is very much greater than normal, as we shall see again in considering water excretion. Thus urea reabsorption will diminish as the rate of urine flow per tubule increases.

To sum up, it may be said that the normal rate of excretion of creatinine and urea is maintained in renal failure even in quite advanced cases, in which probably no more than 10 to 20% of the functioning renal tissue is preserved. This is effected first of all by sustaining a high plasma level of these substances; secondly, by a high rate of filtration per nephron; thirdly, by nocturnal maintenance of maximum possible filtration rate; and, fourthly, by a diminution in the proportion of the urea which the tubules reabsorb.

Conclusion

It may be noted that the *requirements* of urea excretion may be significantly diminished by reducing the protein intake. Pure physiologists mathematically inclined may doubt whether by doing so we are saving the kidney any significant amount of work, since the total osmotic work of the kidney seems to account for only about 1% of its oxygen consumption. "This," as Homer Smith (1951) remarks, "is not to say that the efficiency of the kidney is only 1%; the kidney's efficiency may be very high indeed—it is the thermodynamic approach in terms of final urine that is only 1% efficient." However this may be, clinicians will be more impressed by the fact that in rats whose renal substance was surgically reduced Addis (1948) found that the survival rate was closely related, though in inverse ratio, to their protein intake. I shall continue to recommend a low-protein diet to my renal-failure patients, however competent their adaptive processes. By so doing it would seem that we may increase their survival, and even if we do not achieve that object we may reduce their blood urea. However non-toxic urea may seem to be, anyone who has tried to write the Lumleian Lectures with a blood urea of 80–90 mg. will know from personal experience that it is an impediment to efficiency. But this experiment will be again referred to in its proper place.

(Figs. A and 1–3 are from the paper by Platt *et al.* (1952), by permission of the editor of *Clinical Science*.)

[*The second lecture, with a list of references, will appear in our next issue.*]

*Brod's paper deals with acute nephritis, but his illustration on page 323 showing diurnal fluctuations of creatinine clearance gives data for chronic nephritis ("contracted kidneys").

†For consideration of the validity of endogenous creatinine clearance as a measure of glomerular filtration rate see Brod and Sirota (1948).

AN OUTBREAK OF ENCEPHALITIS, POSSIBLY DUE TO POLIOMYELITIS VIRUS

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[WITH SPECIAL PLATE]

An outbreak of encephalitis affecting eight young children is described. Somnolence, extrapyramidal type of rigidity and tremor, and spastic paralyses were the dominant features of the illnesses of most of the children, while flaccid paralyses were conspicuously absent. On clinical grounds the cases thus bore little resemblance to poliomyelitis, and this diagnosis was hardly entertained until poliomyelitis virus was found in the stools of two of the cases. Even so, after study of the histology of the brain and spinal cord of the two fatal cases, we have been unable to reach any certain conclusion on the aetiology of the encephalitis.

The eight cases occurred in a period of four weeks in the summer of 1949. All were in children aged 5 or younger. All except one lived in an isolated row of fourteen houses in a rural part of Cambridgeshire; the remaining child, who was the first affected (Case 1), lived two miles away. Dr. Derek Simpson was in medical charge of the families, and gave us invaluable help.

Case 1

A baby boy aged 13 months became fretful and feverish on June 17, 1949. On the third day he was noticed to have difficulty in pulling himself up to stand in his cot. On the fourth day he began to have "attacks" lasting a few minutes and coming on about every three hours; in these attacks he went rigid and opisthotonic, the arms quivered, but consciousness was retained. Between attacks he slept peacefully. He vomited once. On the fifth day his head was noticed to be turned to the left side. On the sixth day head tremor appeared and he was admitted to hospital.

Examination on June 22 showed a well-nourished child, conscious but with a curiously expressionless face. His

temperature was normal. His neck was slightly stiff. There was a striking slow rhythmic tremor of head and arms, which were held with elbows, wrists, and fingers semiflexed. Tremor of arms, more pronounced on the left side, disappeared with sleep. The arms showed cogwheel rigidity; the tone of the legs was normal. There was no nystagmus. The fundi were normal. Both knee-jerks were exaggerated, the right more so. The left ankle-jerk was absent. The plantar responses were: left extensor, right equivocal. The cerebrospinal fluid showed: 8 polymorphs and 9 lymphocytes per c.mm.; protein, 50 mg. per 100 ml.; sterile.

During the next two weeks the tremor gradually increased; it became accentuated with voluntary movements, and feeding him became difficult on account of the gross tremor of the head. At times the tremor became so violent that his whole cot shook. On July 5 the movements became wilder still and opisthotonos developed, gradually becoming extreme, while his temperature, which had previously been around 99° F. (37.2° C.), rose to 105° F. (40.6° C.). He became comatose, dying on July 12, the twenty-sixth day of his illness.

Necropsy Findings

Central Nervous System.—There was moderate engorgement of the meningeal blood vessels, but otherwise the only macroscopic abnormalities were two small subependymal haemorrhages (the larger 0.75 by 0.3 by 0.2 cm.) in the floor of the left lateral ventricle near the head of the caudate nucleus, and several rather indefinite greyish foci in the white matter of the cervical spinal cord. Histological sections were prepared of the right frontal cortex, right precentral cortex, right occipital cortex, left basal ganglia, mid-brain, pons, cerebellum, medulla, and spinal cord (nine sections at various levels). Only the section of the mid-brain showed severe changes: in it there were large foci of inflammatory cellular infiltration and neuronal degeneration. Microglial cells and lymphocytes were the predominant cells in the infiltration, and some of the former were swollen with lipoid; the picture was, however, unlike that of the myelinoclastic form of encephalitis. Perivascular "cuffing" was seen in the mid-brain and in the medulla; the cells were mainly lymphocytes, but occasional polymorph leucocytes were seen. In the medulla there was also a single focus of cellular infiltration and degeneration in one olivary nucleus. A similar but smaller focus in a cranial-nerve nucleus was the only definite abnormality seen in the pons. The basal ganglia and cerebral cortex showed no abnormality except hyperaemia and occasional small perivascular haemorrhages. None of the nine sections of spinal cord showed any gross abnormality, but in most of them, and especially in those from the cervical and lumbar enlargements, there was very slight cellular infiltration and neuronal degeneration in the grey matter of the anterior horns, with hyperaemia and haemorrhages, the latter mostly not recent. The changes in the spinal cord were everywhere very much less than those usually seen in poliomyelitis; indeed, they were quite inconspicuous (Figs. 1, 2, and 3, Special Plate). There was slight lymphocytic infiltration of the leptomeninges.

Outside the nervous system the following abnormalities were noted: early bronchopneumonia; an apparently mild otitis media (right), which on culture yielded only a few colonies of non-haemolytic streptococci; acute inflammatory changes in the cervical and bronchial lymph nodes, spleen, and a faucial tonsil; and hyperaemia of the skin of the medial side of the left knee, with conspicuous lymphocytic infiltration of the synovial membrane of the joint.

Poliomyelitis Virus Studies.—Brain: A suspension of various parts of the brain was inoculated intracerebrally into a rhesus monkey, which remained well. *Stools:* A 10% suspension of faeces taken on the nineteenth day of the illness was inoculated intracerebrally and intraperitoneally into a rhesus monkey, which remained well.

Comment.—On the fourth day of the illness there developed rigidity and tremor, giving a picture characteristic of extrapyramidal disease, with a steady progression to a fatal issue. Lower motor neurone paralysis was absent throughout. The clinical picture was an acute Parkinsonism, presumably due to an encephalitis involving the extrapyramidal motor system. Necropsy showed obvious lesions only in the mid-brain, where there was a predominantly lymphocytic infiltration with neuronal degeneration; lesions in the spinal cord were inconspicuous. The virus of poliomyelitis was not isolated either from the faeces or from the brain at necropsy on the twenty-sixth day of the illness.

Case 2

A boy (brother of Cases 3 and 4) aged 2 years became shivery and looked dazed in the afternoon of June 19, 1949; he vomited once that night. On the second and third days he remained up and about, but seemed drowsy, was off his food, and vomited once. On the fourth day his temperature was found to be 103° F. (39.4° C.); although he did not look ill, he was more sleepy and stayed in bed, remaining there for the next seven days. During these seven days he did not utter one word, but slept continuously except when roused, when he would take small amounts of food or drink, relapsing into sleep immediately afterwards. At such times it was noticed that his right hand shook if he tried to grasp a mug. He was incontinent, which was unusual.

On the eleventh day of the illness, the eighth day from the beginning of the somnolent period, he awoke completely recovered; no tremor was now apparent and he could walk normally. Examined for the first time two days later, no abnormal signs could be found.

Comment.—After a three-day mild illness this boy entered a week of continuous somnolence, during which time tremor of one hand was present. Thereafter recovery was abrupt.

Case 3

This patient was a sister of Cases 2 and 4 aged 3 years. On June 22, 1949, she had a mild cold, was abnormally sleepy, and went to bed, where she remained for the next seven days; during the latter half of this week she scarcely spoke, her somnolence being similar to but less profound than that of her brother (Case 2). On the eighth day she got up, when it was noticed that her right arm was not being moved and that her right hand was tremulous. Three days later, on July 3, a squint of the left eye was first noted by the parents.

On examination on July 13 she looked well. There were a slight tremor of the head, right arm, and right leg, and a left sixth-nerve paresis. The right abdominal reflexes were weak. Two months later all these signs had disappeared.

Comment.—Like her brother (Case 2), the girl was somnolent for a week, by the end of which time tremors of head and right arm and leg were apparent, followed by abducent paresis. Recovery was eventually complete.

Case 4

A brother of Cases 2 and 3 aged 9 months was "rather shaky" on the evening of June 25, 1949. Next day coarse tremors of both hands were more pronounced, although he was otherwise well. By the third day the tremor had disappeared.

Virus Studies.—The pooled stools of Cases 2, 3, and 4, collected on July 14, were inoculated intracerebrally, intranasally, and intraperitoneally into a rhesus monkey and caused typical clinical and histological poliomyelitis.

Comment.—The infant had a mild two-day illness with a coarse tremor as the sole symptom. No notice would have been taken of this had it not been that the parents had witnessed the illnesses of the two older children.

Case 5

A baby girl (sister of Case 6) aged 18 months became abnormally sleepy on June 22, 1949. Next day she

remained lying down all day, sleeping continuously except when roused to take food. This somnolence persisted over the next seven days, during the whole of which time she uttered no word. She was incontinent, which ordinarily she was not. On the fifth day it was seen that when she was roused she could not use her left hand, and that her left arm and left leg shook if she tried to use them. Her head was bent towards the left shoulder.

When admitted to hospital on June 30 she was afebrile and consciousness was normal. Slight neck stiffness and spastic hemiplegia with hyperreflexia of left arm and leg were present, and a coarse tremor developed in these limbs if she was disturbed. The plantar reflexes were: right extensor, left normal. The cell and protein content of the cerebrospinal fluid were normal.

Recovery of movement of left limbs was gradual. By July 18 she was moving all limbs fairly well, but slight intention tremor was present in both hands. At six weeks from the onset she had recovered completely.

Virus Studies.—A 10% suspension of a stool collected on the fifteenth day of illness was inoculated intracerebrally, intranasally, and intraperitoneally into two rhesus monkeys; both developed clinical and histological poliomyelitis.

Comment.—The illness began with somnolence, which lasted for a week. On the fifth day there developed a spastic hemiplegia and tremor affecting the left side, with transient pyramidal signs (extensor plantar reflex) on the right side. Recovery was complete. Poliomyelitis virus was isolated from faeces.

Case 6

This patient, a sister of Case 5, aged 5 years, became feverish on the evening of July 1, 1949, and refused to eat. Next day she was well and remained so until the 4th, when she complained of headache and went to bed.

On admission to hospital on July 5 her temperature was 103° F. (39.4° C.), and consciousness was normal. There was no neck stiffness. Slight tremor of head and of outstretched hands was present, increased by intention. Tendon reflexes were normal. The cerebrospinal fluid showed: 6 polymorphs and 9 lymphocytes per c.mm.; protein, 20 mg. per 100 ml.

The patient became afebrile by July 7, and thereafter the tremor gradually disappeared; by the end of the third week it was only just discernible, and at seven weeks recovery was complete.

Comment.—This was a mild febrile illness of biphasic type, the only neurological sign being tremor. Virus studies were not made.

Case 7

A girl aged 5 had a headache and was feverish on the evening of July 3, 1949. On the 4th she slept all day, ate nothing, and continued to complain of headache and feeling sick. By the third day she had recovered completely.

Comment.—This was a transient febrile illness, with headache as the dominant symptom. Virus studies were not made.

Case 8

A boy aged 5 awoke on the morning of July 14, 1949, complaining of headache. He lay about all day, ate little, and vomited once. On the next day he remained up at first, but in the afternoon went to lie down, where shortly afterwards his mother discovered him completely unresponsive, though still just capable of swallowing a little water.

He was admitted to hospital on July 16. His temperature was 104.8° F. (40.5° C.). He was in deep coma. His trunk was opisthotonic, and his limbs were rigid and extended, with wrists flexed. His eyes deviated upwards and inwards; the left pupil was larger than the right; the fundi were normal. Tendon reflexes and abdominal reflexes were absent; plantar reflexes were extensor. The cerebrospinal fluid showed: 20 polymorphs and 61 lymphocytes per c.mm.; protein, 20 mg. per 100 ml. Twitchings of limbs developed and he died in hyperpyrexia on the third day of his illness, a few hours after admission.

Necropsy

Central Nervous System.—There was general hyperaemia of the grey matter throughout the brain and cord, and of the leptomeninges (especially over the temporal lobe). The mid-brain was soft and bulged abnormally on section, as also did the spinal cord at all levels. The claustrum appeared abnormally large, especially on the right side. These were the only macroscopic abnormalities in the central nervous system. Histological sections included 11 sections from various parts of the cerebral hemispheres, 6 from the basal ganglia, 10 from the spinal cord; 3 from the cerebellum, 2 from the medulla, and 1 each from the hypothalamic region, mid-brain, and pons. A Gasserian ganglion and a dorsal root ganglion were also sectioned. Microscopical examination showed an encephalomyelitis with maximal involvement of the mid-brain (especially the substantia nigra) and the hypothalamus. Conspicuous changes were also seen in the olivary nuclei of the medulla and slight but definite changes in the reticular formation of the pons. Except for a few foci of inflammation and neuronal degeneration in the optic thalami and lenticulate nuclei, especially near to the lateral ventricles, the basal ganglia had escaped. No definite lesion other than one petechial haemorrhage was seen in the cerebral hemispheres. In the spinal cord one section of the cervical enlargement showed severe involvement of an anterior horn; in this one section the histological picture was characteristic of poliomyelitis (Figs. 4 and 5), but none of the nine other sections at various levels down to the lumbo-sacral region showed any conspicuous abnormality. There appeared, however, to be slight cellular infiltration in the anterior horns of the upper cervical region and lumbar enlargement. In the posterior root ganglion and the Gasserian ganglion there was considerable cellular infiltration (apparently lymphocytic) with focal degeneration of neurones.

In the affected parts of the central nervous system there were two main features: first, infiltration of the grey matter with microglia cells and polymorphonuclear leucocytes, and perivascular cuffing due to the presence of numerous lymphocytes and macrophages—together with a variable number of polymorphonuclear leucocytes—in the Virchow-Robin spaces; and, secondly, degeneration of neurones, with neuronophagia. The meninges of the brain and spinal cord showed a slight degree of infiltration with lymphocytes and macrophages.

The only definite abnormalities outside the nervous system were as follows: one small focus of cellular infiltration in the myocardium of the interventricular septum; partial collapse, congestion, some oedema, and intra-alveolar haemorrhage in the lungs; a considerable excess of neutrophil leucocytes in the spleen; pus in one tonsillar crypt, with leucocytic infiltration in the adjacent lymphoid tissue; reactive hyperplasia in the rather large cervical lymph nodes; petechial haemorrhages in the thymus; congestion of thyroid, pituitary, and pancreas; threadworms in appendix; inequality in the size of the pupils, the left being decidedly larger than the right.

Virus Studies.—A suspension of various parts of the brain was inoculated intracerebrally into two rhesus monkeys; both remained well.

Comment.—This was a fulminating infection leading to the picture of decerebrate rigidity and death on the third day. Poliomyelitis virus was not isolated from the brain.

The Table on page 1320 summarizes these case records.

Additional virus studies were carried out by Dr. N. B. Finter, of the Department of Pathology, Cambridge. Specimens of blood and/or cerebrospinal fluid from Cases 1, 5, 6, and 8 were inoculated both intracerebrally and intraperitoneally into mice, rabbits, guinea-pigs, and hamsters,

Clinical Features and Virus Findings in Eight Children with Encephalitis

Case No.	Sex	Age in Years	Date of Onset	Main Clinical Features	C.S.F.: Cells per c.mm.	Outcome	Poliomyelitis Virus Findings
1	M	1 1/12	17/6/49	Acute Parkinsonism	8 polys. 9 lymphs.	Death 26th day	Brain and stool—negative
2	M	2	19/6/49	Somnolence; tremor	—	Recovery	Pooled stools —positive
3	F	3	22/6/49	Somnolence; tremor; sixth-nerve paresis	—	,,	
4	M	9/12	25/6/49	Tremor	—	,,	
5	F	1½	22/6/49	Somnolence; tremor; spastic hemiplegia	None	,,	Stool—positive
6	F	5	1/7/49	Tremor	6 polys. 9 lymphs.	,,	—
7	F	5	3/7/49	Headache; vomiting	—	,,	—
8	M	5	14/7/49	Decerebrate rigidity	20 polys. 61 lymphs.	Death 3rd day	Brain—negative

and into the amnions and yolk sacs of eggs. Samples of both brain and spinal cord tissue from Case 8 were similarly treated. No viral agent was isolated.

Epidemiological Findings

An infecting agent common to the cases was inferred on the following grounds: (1) all eight cases occurred in a period of four weeks; (2) with the exception of Case 1 all the affected children came from four families living in an isolated row of houses; and (3) there was an obvious similarity between the illnesses—for instance, tremor was a prominent symptom of Cases 1, 2, 3, 4, 5, and 6, while the histology of the brains of the two fatal cases (Nos. 1 and 8) was essentially similar. Only in Case 7 is there some doubt; this 5-year-old girl had a mild two-day illness with fever, headache, and vomiting—symptoms which in the circumstances were suspicious but not conclusive of a mild encephalitis.

Age Distribution.—All eight children were aged between 9 months and 5 years. This represented a high incidence among the children living in the row of houses, where seven children (Cases 2 to 8) of the total of 21 below the age of 6 years were affected; adults were not affected. A house-to-house call was made to find out whether there had been any unexplained minor illnesses. The only cases discovered were on the farm where Case 1 lived. His two brothers had suffered from fever and sore throats, clinically a follicular tonsillitis, at the time of onset of their brother's illness. A lad who worked on the farm had fever, severe headache, and backache on July 15 but recovered on the next day. This illness might have been due to the agent responsible for the encephalitis.

Mode of Spread.—There was ample opportunity for contact among the seven children (Cases 2 to 8) living in adjacent houses, and the pattern of the epidemic (see Diagram) is compatible with a case-to-case spread, with a

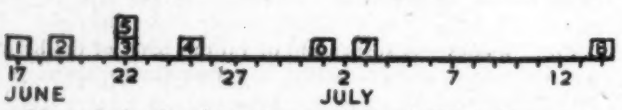

Diagram showing dates of onset of encephalitis in Cases 1–8.

suggestion of groups of cases occurring at intervals of about 7 to 10 days—Cases 2, 3, 4, and 5, followed by Cases 6 and 7, followed by Case 8. Case 1 was the son of a farm worker living on a farm two miles from the homes of the other cases, with whom he had no direct contact. Three possible connexions existed, however: first, this farm supplied milk to the homes of all the cases; secondly, the milk roundsman himself was a contact of all the cases; and, thirdly, the father of Cases 5 and 6 worked on this farm, occasionally saw Case 1, and sometimes milked the cows. Although neither of these men had had any recent illness, in view of the other evidence pointing to a case-to-case spread it is conceivable that one of them was a symptomless carrier of the encephalitogenic agent.

Suspicion naturally fell on milk as the vehicle of infection when it was found that the common milk supply came from the farm where Case 1 lived, that it was prepared under bad hygienic conditions, and that it was not pasteurized. However, this milk was supplied to several hundred people, including 200 schoolchildren, in the district, amongst whom only this localized outbreak occurred, so that a milk-borne agent was improbable.

Spread of infection from faeces could not be excluded; the households concerned used pail privies and buried the contents in the garden. At the time flies were not numerous.

These and many other lines of inquiry were pursued, but no conclusion was reached regarding the primary source of infection, and it remained doubtful whether infection was first introduced to the farm and spread from there, or whether it was introduced simultaneously to the farm and to the families living in the isolated row of houses. Spread by contact was the likeliest explanation of the later cases in families in these houses.

Discussion

The nature of the encephalitis rests upon evidence of four kinds—the pattern of the clinical illness, the epidemiological pattern, the virus findings, and the neurohistological findings. Of the known forms of encephalitis three must be considered—poliomyelitis, lethargic encephalitis, and that group comprising Japanese B, Australian X, St. Louis, and equine encephalitis.

Poliomyelitis

Since the clinical signs in the affected children were predominantly those of somnolence, extrapyramidal type of rigidity, and tremor, with pyramidal signs such as spastic paralyses, and since there was a conspicuous absence of cranial, bulbar, or spinal paralyses (save for a single example of an abducent paresis), poliomyelitis was not seriously considered until this virus was found in the stools

LEGENDS TO PLATE

S. MARSHALL AND K. S. MILLINGEN

FIG. 1.—Hilar gland. Note pigment-containing macrophages, stromal oedema, diffuse and focal infiltration with abnormal "monocytic" cells. (H. and E. ×500.)

FIG. 2.—Liver. Necrosis and fatty change in liver cells; loss of normal architecture; abnormal "monocytes," some with hyperchromatic nuclei. (H. and E. ×400.)

FIG. 3.—Spleen. Many pigment cells; diffuse infiltration with abnormal "monocytes," one in top left corner showing nuclear fenestration. (H. and E. ×500.)

FIG. 4.—Kidney. Note tubular degeneration; granular debris within tubules; monocytic cells in capillaries and stroma. (H. and E. ×500.)

H. J. RICHARDS

FIG. 1.—Young cellular fibrous tissue of painful tender nodules. (H. and E. ×105.)

FIG. 2.—More mature tissue of the contracture, which is less cellular; increased intercellular tissue and laying down of collagen. (H. and E. ×105.)

R. PLATT: ADAPTATION IN RENAL FAILURE

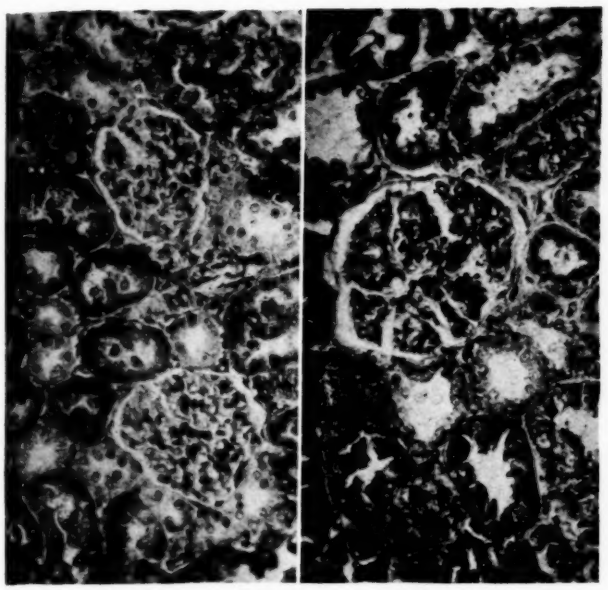

FIG. 1a FIG. 1b

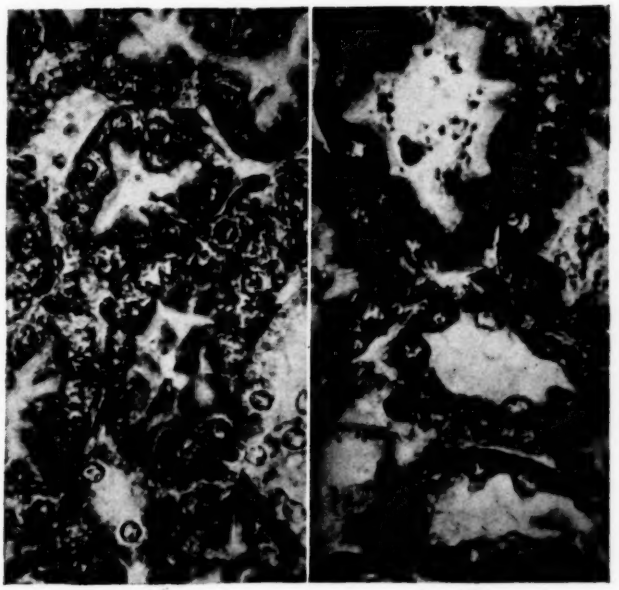

FIG. 2a FIG. 2b

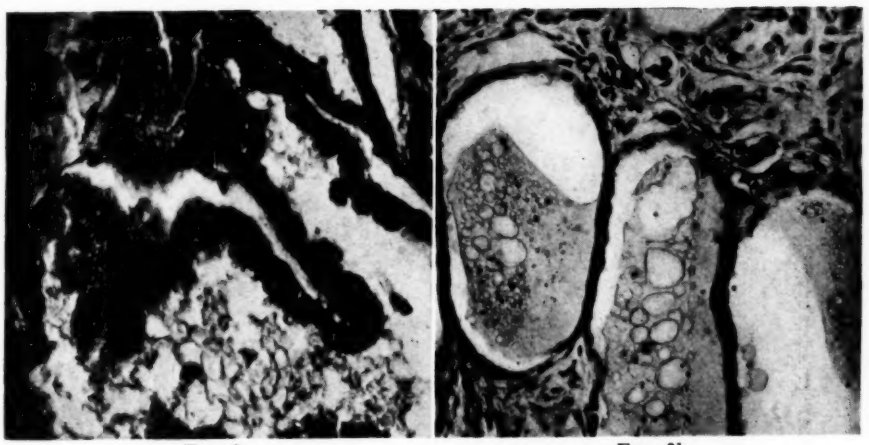

FIG. 3a FIG. 3b

FIG. 1.—(*a*) Normal rat kidney; (*b*) renal remnant (see text), showing hypertrophy of glomerulus and tubules. (Masson's trichrome. ×220.)

FIG. 2.—(*a*) Intermediate part of proximal tubule (normal rat); (*b*) same from renal remnant, showing hypertrophy and dilatation. (Masson's trichrome. ×450.)

FIG. 3.—Human chronic pyelonephritis. (*a*) Tubules showing hypertrophy and (*b*) dilatation with flattened atypical epithelium. (Masson's trichrome. ×220.)

S. MARSHALL AND K. S. MILLINGEN: CASE OF INFECTIOUS MONONUCLEOSIS

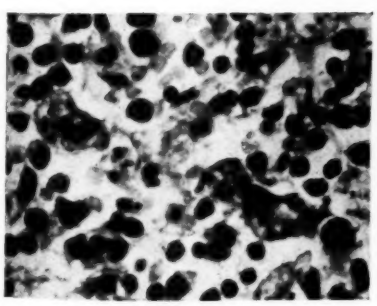

FIG. 1

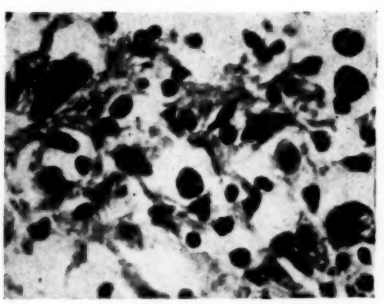

FIG. 2

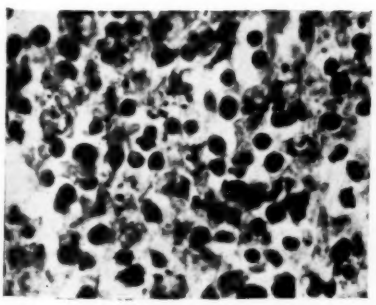

FIG. 3

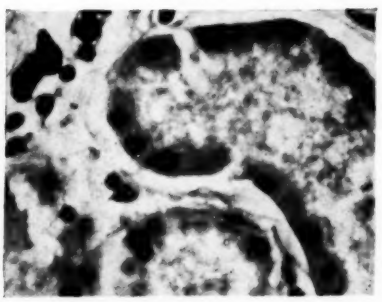

FIG. 4

H. J. RICHARDS: DUPUYTREN'S CONTRACTURE

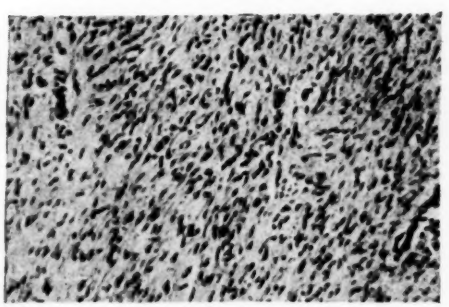

FIG. 1

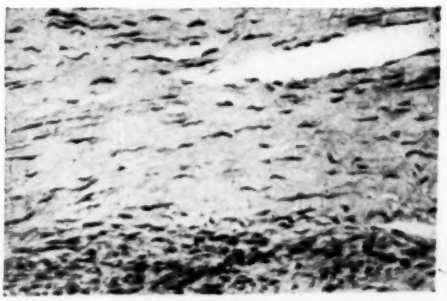

FIG. 2

A. M. BARRETT, D. GAIRDNER, AND A. M. McFARLAN: ENCEPHALITIS POSSIBLY DUE TO POLIOMYELITIS VIRUS

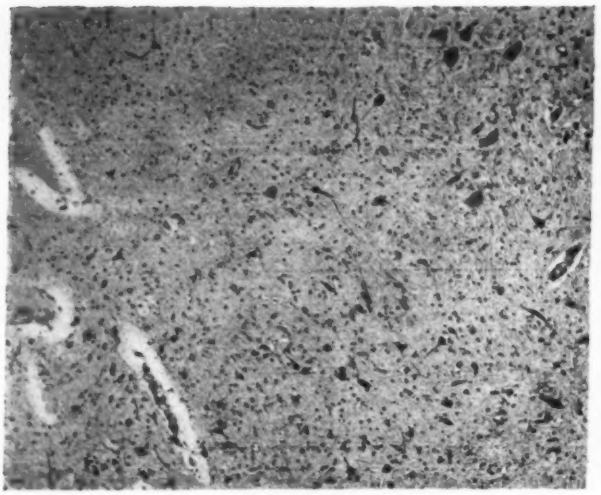

FIG. 1

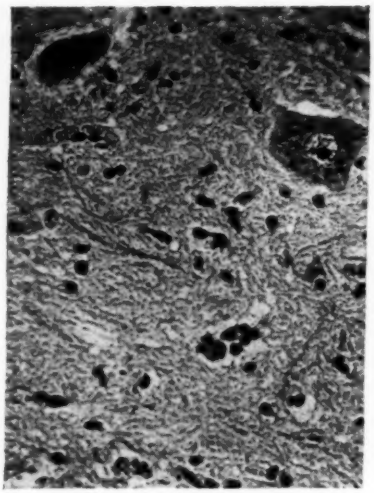

FIG. 2

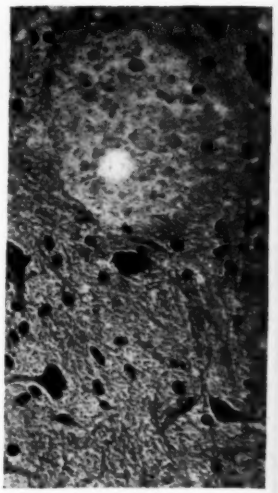

FIG. 3

FIG. 1.—Case 1. Most affected part of spinal cord (cervical). Part of an anterior horn shown at top right. Neurones relatively well preserved; very little cellular reaction. Blood vessels at bottom left surrounded by wide but empty Virchow–Robin spaces. (Ehrlich's H. and E. ×65.) FIG. 2.—Case 1. High-power view Fig. 1. Slight cellular infiltration in anterior horn, with well-preserved neurones. (Ehrlich's H. and E. ×640.) FIG. 3.—Case 1. High-power view Fig. 1. Many neurones shrunk and deep-staining; little cellular infiltration. Circular pale focus possibly petechial haemorrhage in which erythrocytes mostly disintegrated. (Erhlich's H. and E. ×640.)

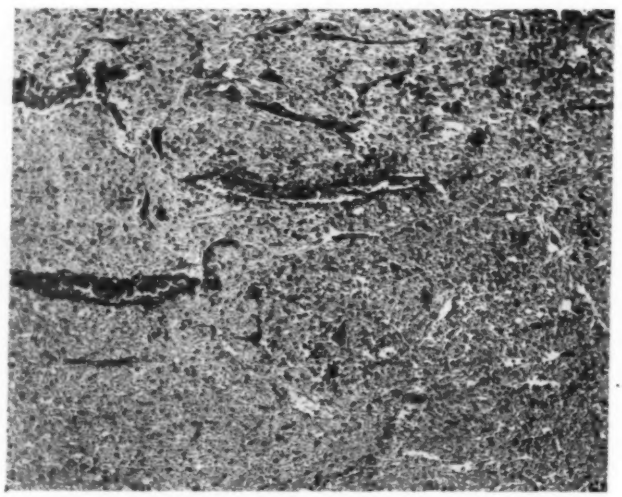

FIG. 4.—Case 8. The most affected part of spinal cord. Greater part of an anterior horn included at top right. Note degree of cellular infiltration and disappearance of most of the neurones. (Ehrlich's H. and E. ×65.)

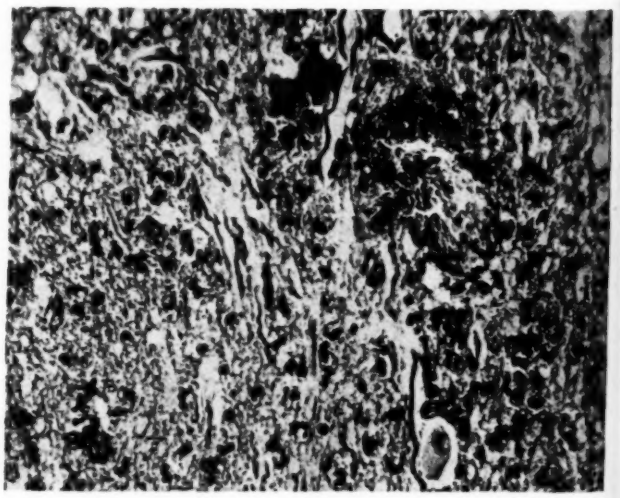

FIG. 5.—Case 8. High-power view of part of the anterior horn seen in Fig. 4. Most cells are microglial. Irregular darkly stained object at top middle is a degenerating neurone showing neuronophagia. (Ehrlich's H. and E. ×640.)

D. R. C. WILLCOX: HAEMOLYTIC ANAEMIA AND RETICULOSES

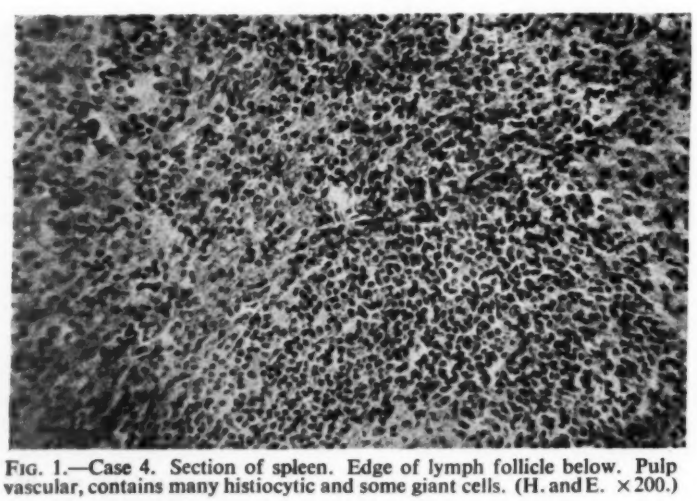

FIG. 1.—Case 4. Section of spleen. Edge of lymph follicle below. Pulp vascular, contains many histiocytic and some giant cells. (H. and E. ×200.)

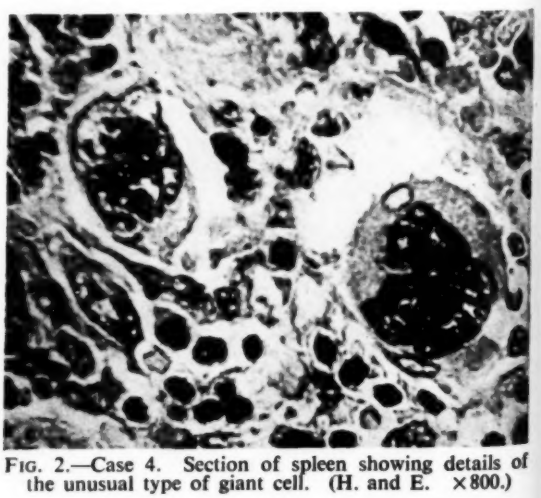

FIG. 2.—Case 4. Section of spleen showing details of the unusual type of giant cell. (H. and E. ×800.)

of two of the cases. The idea of poliomyelitis existing in an encephalitic form dates back to Strümpell (1885), who first used the term polio-encephalitis to describe the acute febrile illness of infancy associated with convulsions and followed by spastic hemiplegia. This is now known to have nothing to do with poliomyelitis (Wyllie, 1948). Excluding such cases, occasional cases have been reported (for example, Case 57 of Medin, 1898) in which a patient had suffered an acute illness with somnolence, coma, convulsions, ataxia, or pyramidal effects as prominent features, and in which poliomyelitis has either been surmised on account of the existence at the time of a poliomyelitis epidemic (Peabody, Draper, and Dochez, 1912) or, less frequently, has been proved at necropsy (Jennings, Hamilton-Paterson, and MacCallum, 1949; Kelleher, Bratton, and MacCallum, 1949). Such cases are rare, and no record has been found of any consecutive series of cases presenting a purely encephalitic picture. Two minor clinical points are worth comment. The absence of any pleocytosis in the cerebrospinal fluid of Case 5 on the eighth day of the illness would be unusual in poliomyelitis. On the other hand, the biphasic illness of Case 6 was suggestive of poliomyelitis.

Epidemiologically the course of the outbreak was compatible with, though not typical of, poliomyelitis: it occurred in summer, only children of 5 or under were affected, and 7 out of 21, or one-third of one group of children, were ill—a heavier incidence than has been usual in recent poliomyelitis outbreaks in Britain.

The significance to be attached to the finding of poliomyelitis virus in the faeces of one patient and the pooled faeces of three others is difficult to assess, since we do not know the incidence of poliomyelitis virus in the faeces of the general population at the time of the outbreak. That the incidence in Cambridgeshire was probably low may be surmised from the fact that there was a low incidence of poliomyelitis in Cambridgeshire in 1949 and in previous years. Up to the time of the outbreak of encephalitis no case of poliomyelitis had occurred in the vicinity, but on July 17 a typical case occurred in a 20-year-old woman who lived a mile from the farm where Case 1 lived and who visited this farm once a week to pay for the milk she obtained there. The failure to demonstrate virus in brain tissues from the two fatal cases is not of great significance, since in the experience of Dr. F. O. MacCallum (personal communication) successful isolation is achieved in only about 50% of fatal cases.

The histological differentiation of the various types of encephalomyelitis is based upon the *distribution* and the *character* of the histological changes in the central nervous system. In poliomyelitis the lesions are restricted to the grey matter, and they are found (Bodian, 1949) in the spinal cord, especially in the anterior horns; in the brain stem, especially around the fourth ventricle, but not in the ventral part of the pons or in the inferior olive; in the mid-brain and hypothalamus; and sometimes in the precentral gyrus but not elsewhere in the cerebral cortex. Except for focal lesions in the inferior olivary nuclei, all of the lesions in the two fatal cases described above fall within the normal territory of poliomyelitis as thus defined. Involvement of the posterior root ganglion and Gasserian ganglion as in Case 8 is also seen in poliomyelitis. Thus it is seen that if no regard be paid to the relative severity of involvement of different parts of the affected territory, the *distribution* of the lesions in the two fatal cases closely resembles that in poliomyelitis. The slightness of the changes in the spinal cord compared with those in the brain is, however, a serious objection to the diagnosis of poliomyelitis. Even in cases of poliomyelitis which show little or no clinical evidence of cord involvement it seems invariable to find conspicuous histological changes in the cord (Jennings *et al.*, 1949; Kelleher *et al.*, 1949); yet none of the nine sections from various levels of the cord in Case 1, and only one of the ten sections in Case 8, showed more than very slight changes.

In *character* as distinct from distribution, the lesions in the two fatal cases are identical with those usually seen in poliomyelitis: neuronal degeneration is conspicuous, neuronophagia is present; the most severely affected foci of grey matter are heavily infiltrated with microglia cells, which in some places have taken up fairly large amounts of lipoid matter; and the perivascular cuffs of cells include lymphocytes and a small number of polymorphonuclear leucocytes but very few, if any, plasma cells.

From the histological point of view, therefore, the only findings which are opposed to the diagnosis of poliomyelitis are, first, the slightness of involvement of the spinal cords; and, secondly, the presence of focal lesions in the inferior olivary nuclei. Since these features were present in both of the only two cases examined, and since they are both very unusual in poliomyelitis, if the epidemic is attributed to infection with poliomyelitis virus, it appears necessary to assume either that the virus was possessed of unusual properties or that some unusual environmental factor was affecting the response of the children to infection.

Lethargic Encephalitis

Although the remarkable somnolence shown by three of the cases at once brought this disease to mind, the clinical picture as a whole differed in many respects from the descriptions of this disease. Thus the onset was sudden rather than insidious, the sole example of a cranial nerve palsy was an abducent palsy, and the cells in the cerebrospinal fluid were 25 to 50% polymorphonuclears, whereas the pleocytosis is lymphocytic in lethargic encephalitis even in acute cases (Perdrau, 1922). Finally there were no sequelae in the six patients who survived.

Epidemiologically also the facts are against this diagnosis. It occurred in summer and affected children only, with multiple cases in two families, whereas outbreaks of lethargic encephalitis have been confined to winter or spring, young children are less often affected than adults, and multiple cases in a family are rare.

The histological lesions of encephalitis lethargica as seen in the outbreaks which followed the first world war were usually maximal in the mid-brain, the upper part of the pons, and the basal ganglia; slighter changes were commonly seen in the medulla (MacNalty, 1921). Changes were rarely seen in the spinal cord, and at most were slight. Involvement of the cerebral cortex has been described (Buzzard and Greenfield, 1919; Watson, 1920), but is not characteristic; nor were the degenerative changes in the Purkinje cells of the cerebellum seen once by Marinesco (1918). This distribution of lesions is closely similar to that seen in our two fatal cases; in both of the latter, however, changes were present in the spinal cord, and although these cord changes were slight compared with those usually seen in poliomyelitis, yet they were apparently more extensive in Case 1, and more severe in Case 8 than was normal in encephalitis lethargica. The distribution of the lesions in our cases is nevertheless consistent with the diagnosis of encephalitis lethargica.

However, when the histological characteristics of the lesions are considered as well as their distributions, it seems unlikely on histological grounds that our cases were due to encephalitis lethargica. The appearance of the foci of microglial infiltration in the grey matter with severe degeneration of neurones and conspicuous neuronophagia; the presence of polymorphonuclear leucocytes and the absence of plasma cells amongst the inflammatory cells; the degree of cellular infiltration in the meninges—all these speak for an inflammatory reaction more intense than that usually seen in encephalitis lethargica. The character of the lesions is undoubtedly more like poliomyelitis than encephalitis lethargica.

St. Louis, Equine, Japanese B, and Australian X Encephalitis

It is generally agreed that these four epidemic types of encephalitis due to neurotropic viruses are closely related, there is much similarity in their symptomatology and neuro-

histology, and, in addition, the viruses of some members of this group have antigens in common. Epidemics caused by this group of virus agents have occurred in hot weather, have sometimes chiefly affected young children, and have been associated with a clinical picture quite similar to our cases. In this group of encephalitides the histological lesions are often widely scattered throughout the central nervous system. Although the brain stem is perhaps the favourite location, the cerebral hemispheres, cerebellum, and spinal cord may all be involved; the white matter as well as the grey matter is affected; and there is more meningeal reaction than in encephalitis lethargica. In Japanese B encephalitis destruction of Purkinje cells in the cerebellum is a striking feature. In view of the restriction of the lesions to the grey matter in our two fatal cases, and of the absence of involvement of the cerebral cortex or cerebellum, it is impossible to regard the distribution of the lesions as at all characteristic of this group of infections; nevertheless, on histological grounds it is not impossible that our cases might belong to that group. The character of the lesions also is consistent with such a diagnosis, but again there is nothing distinctive about it. The Purkinje cells in our cases did not appear to be reduced in number, and although some of them showed apparent degenerative changes, similar changes can be seen in control sections of the cerebellum of children who did not die of encephalitis.

In this group of encephalitides the virus can often be isolated with relative ease by intracerebral inoculation of mice; the negative findings in this respect therefore are worth noting.

Summary and Conclusions

An outbreak of encephalitis is described; eight children were affected, with two deaths.

Clinically the pyramidal and extrapyramidal motor systems were predominantly affected, and lower motor neurone lesions (with one minor exception) did not occur.

The histology of the brains of the two fatal cases was consistent with poliomyelitis; on the other hand, the lesions in the spinal cords were not nearly so prominent as is the rule in poliomyelitis.

Poliomyelitis virus was recovered from the stools of one case, and from a pool of the faeces of three others.

In comparing the clinical, epidemiological, viral, and neurohistological findings in our cases with those of other known encephalitides, we conclude that this outbreak was either one of poliomyelitis with several most unusual features or was an example of some hitherto undescribed type of encephalitis. We slightly favour the former view.

Our thanks are due to Dr. F. O. MacCallum, Director of the Virus Research Laboratory of the Public Health Laboratory Service, and to Dr. N. B. Finter, of the Department of Pathology, Cambridge, for the virus studies; and to Mr. S. W. Patman for the photomicrographs.

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HAEMOLYTIC ANAEMIA AND RETICULOSES

BY

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(From the Department of Clinical Pathology, Guy's Hospital London)

[WITH SPECIAL PLATE]

Haemolytic anaemia associated with various neoplastic processes is a recognized but not a common clinical entity (Davidson, 1932; Waugh, 1936; Singer, 1940: Stats, Rosenthal, and Wasserman, 1947). In many of these cases the haemolytic picture is merely incidental to the malignant process. Lucey (1939) and Pollard (1948) have recorded single cases in which haemolytic anaemia presented, apparently of idiopathic type, and the neoplastic association was found only at necropsy. Both these were cases of carcinomatosis.

Four cases of haemolytic anaemia are recorded here. In two of them clinical evidence of malignant disease (lymphosarcoma and reticulum-cell sarcoma) first appeared several months after the onset of haemolytic anaemia. In another case reticulo-endothelial changes were found only at post-mortem examination. These cases appeared to illustrate some points of interest in the clinico-pathological picture, and also in the possible mechanism of production of this type of anaemia.

Case 1

An unmarried woman aged 40 had lived a healthy and active life. Menstruation had ceased 18 months previously. She complained of lassitude for five weeks, and of dyspnoea and palpitations for two weeks. The severity of her symptoms had increased rapidly up to the time of her admission to hospital.

On admission on June 14, 1949, she was slightly dyspnoeic at rest. The skin and mucous membranes were very pale and slightly icteric, as were the sclerae. The apex beat was just beyond the mid-clavicular line, and a blowing systolic murmur was heard in this area. Her temperature was 99.8° F. (37.7° C.), pulse 100, and respirations 22. There were no other abnormalities on physical examination. The spleen was not palpable.

Investigations.—Urine: excess of urobilin, no bilirubin, no haemoglobin. Blood: haemoglobin, 33% (5.15 g.); red cells, 1,200,000; colour index, 1.3; M.C.D., 8 μ; P.C.V., 18%; M.C.V., 150 μ^3; M.C.H.C., 29%; M.C.A.T., 3.3 μ; reticulocytes, 24%; late normoblasts 3 per 100 white cells; the red cells showed anisocytosis and slight anisochromia with numerous polychromatic cells and macrocytes; white cells, 9,800 (polymorphs 70%, eosinophils 1%, basophils 1%, lymphocytes 21%, monocytes 1%, myelocytes 4%, metamyelocytes 2%); the polymorphs showed a left shift. The red-cell fragility was slightly increased: haemolysis started at 0.55% saline, and was complete in 0.30% saline. The direct Coombs test was positive. Chemical: serum bilirubin, 2.25 mg. per 100 ml.; van den Bergh direct test, delayed response; empirical liver tests (thymol turbidity and flocculation and colloidal gold) were negative; test meal, histamine-fast achlorhydria.

A diagnosis of acute haemolytic anaemia of unknown cause was made. The patient was transfused on three occasions without incident. A course of penicillin was given to combat any possible infective cause of the haemolysis. She continued pyrexial and jaundiced for some time, but was sufficiently improved by August 2 to be discharged, her haemoglobin then being 13.26 g. per 100 ml.

When seen at the out-patient department on September 28 and October 8 and 26 her haemoglobin was falling. In

addition palpable left axillary lymph nodes were noted, and an ill-defined mass was felt in the abdomen. She was now found to be rhesus-negative, and to have produced low-titre antibodies, presumably from her earlier transfusions. The direct Coombs test was still positive, and this could not be attributed to the effects of transfusion more than three months previously.

She was readmitted on November 7. The blood, no longer macrocytic, showed: haemoglobin, 8.58 g.; red cells, 3,000,000; reticulocytes, 5%. The urine contained an excess of urobilin. Further investigations showed no occult blood in the stools, normal radiographic appearances following barium meal and enema, and a normal intravenous pyelogram. A probable diagnosis of a malignant mass in the mesentery was made, and laparotomy was performed on December 19. The mass lay in the mesentery; it consisted of matted glands, and other retroperitoneal lymph nodes were also enlarged. A biopsy was taken and the abdomen closed. In spite of transfusions, now with rhesus-negative genotyped blood, the haemolytic process increased rapidly and her general condition deteriorated. She died on January 3, 1950.

Section of the biopsy material showed lymph-node tissue with severe reticular hyperplasia suggestive of reticulum-cell sarcoma.

Post-mortem Findings.—The main finding was enlargement of all the abdominal lymph nodes, a number of which were matted to form a definite mass in the mesentery. The nodes were white and homogeneous on section. Similar white areas were scattered over the lower part of the ileum. The liver was pale and enlarged. The spleen was enlarged but rotated and fixed by adhesions above the costal margin. Histologically the lymph nodes showed complete loss of normal pattern, with much lymphoid and reticulum-cell hyperplasia and occasional giant cells. Numerous mitotic figures were seen. There was no fibroblastic activity or erythrophagocytosis. The spleen was grossly congested and the widely spaced cellular elements appeared normal. The liver was infiltrated with lymphoid and reticulum cells around the portal tracts and in two diffuse areas. The picture was that of reticulum-cell sarcoma.

Comment.—This case shows a typical acute haemolytic anaemia preceding clinically the development of signs of a reticulum-cell sarcoma.

Case 2

A widow aged 68 had suffered from anaemia since 1930. Treatment with both liver and iron had had little effect, but later myxoedema was diagnosed, and she had received thyroid extract, 1 gr. (65 mg.) daily, for several years.

She was admitted on February 23, 1949, for anaemia and recent precordial pain, following a report of abnormal white cells seen during a routine count. She was considered still to be myxoedematous, and the dose of thyroid was increased. A blood picture showed: haemoglobin, 68% (10.61 g.); red cells, 3,300,000; M.C.D., 7.5 μ; and, later, haemoglobin 68% with 1% reticulocytes. The film appearances showed definite spherocytosis and the red-cell fragility was greatly increased, haemolysis starting in 0.65% saline and being complete in 0.35%. The Coombs test was negative, and the sternal marrow normal. She improved with transfusion and increased thyroid dosage, and was discharged on March 30. The B.M.R. had risen from −20 to −4.

Subsequently she sought attention elsewhere, and was found to have an abdominal tumour (Hb, 7.7 g.; red cells, 2,700,000). A laparotomy was performed and a mass involving the ileo-caecal junction and the glands at this site was resected. This mass consisted of the terminal 4 in. (10 cm.) of the ileum and a portion of caecum. The mucosa on either side of the ileo-caecal valve showed nodular thickening up to 1 cm. in depth in the ileum and 2 cm. in the caecum. The cut surface was white and neoplastic. Two enlarged lymph nodes were found, the larger being 1 cm. in diameter.

On section the nodules in the caecum and ileum consisted of lymphoid tissue lying in the submucosa and infiltrating the muscular layers. The lymph nodes showed loss of normal pattern. There was a diffuse and uniform lymphoid hyperplasia. Most of the cells were small with darkly staining nuclei. There was no fibrosis or any evidence of erythrophagocytosis. The picture was that of lymphosarcoma.

Post-operative progress was satisfactory. The patient was well six months later. The anaemia had improved, but a mild degree was still present: Hb, 10.8 g. per 100 ml.; red cells, 3,800,000. Red-cell fragility: haemolysis of the patient's cells started in 0.52% saline and was complete in 0.44%; haemolysis of normal control cells started in 0.44% saline and was complete in 0.36%. The Coombs test was again negative. Re-suspension of the patient's washed cells with bovine albumin produced no agglutination.

Comment.—The anaemia in this case, although mild and chronic, was of classical spherocytic haemolytic type. The associated lesion was a mass showing the characteristic features of lymphosarcoma. The question arises, particularly in view of the negative serological findings, whether this is a chance association, and the patient suffers from congenital (familial) haemolytic anaemia. This cannot be definitely excluded. Such a diagnosis would, however, introduce a third condition in this case. In addition there is no family history, although no relatives were available for investigation. The patient had been observed haematologically for many years without spherocytosis or other evidence of haemolysis being noted until a few months before the malignant process became apparent. Her age was 68, and she gave no history of jaundice or of marked periodicity in her anaemia. It therefore seems reasonable to suppose that the haemolytic process was of recent onset and related to the development of the lymphosarcoma.

Case 3

A man aged 28 had been fit until 1948. He was married and had served in the Navy during the recent war. In 1948 he complained of an enlarged gland in the left posterior triangle. A biopsy was taken and a diagnosis of Hodgkin's disease was made. He received a course of deep *x*-ray therapy to the neck (four exposures). The gland subsided and he returned to work. In June, 1950, he started to complain of lassitude and breathlessness, and he noticed an enlarged gland in the left axilla. He was admitted to hospital on August 23. Pallor, dyspnoea, and slight jaundice were noted. There were enlarged, firm, and discrete glands in the left axilla.

Investigations.—The van den Bergh direct test gave a biphasic response. Serum bilirubin was 2.2 mg. per 100 ml. Blood: haemoglobin, 4.4 g. per 100 ml.; red cells, 1,120,000; white cells, 15,700 (polymorphs 72%, stab 5%, lymphocytes 13%, monocytes 5%, metamyelocytes 5%); there was marked polychromasia and macrocytosis with moderate numbers of late normoblasts; reticulocytes, 24.8%; red-cell fragility normal; Group O, Rh-positive; Coombs test negative. Urine showed an excess of urobilin. Wassermann reaction and Kahn test negative. *X*-ray film of chest and long bones normal. Blood culture sterile. Sternal marrow cellular and normoblastic.

The patient was treated with transfusions, and a biopsy of an axillary lymph node was taken. On September 26 he was transferred to Guy's Hospital. On examination there was pallor but no jaundice. The tip of the spleen was just palpable. Enlarged glands were present in the left posterior triangle and there was a recent biopsy scar in the left axilla. Haemoglobin at this time was 8.7 g. per 100 ml. The film showed much anisocytosis and polychromasia but little poikilocytosis. The presence of small dark-staining cells was also noticed. The appearances were suggestive of spherocytosis. Red-cell fragility, however, was normal. P.C.V., 28%; M.C.V., 112 μ^3; M.C.T., 2.4 μ; thickness–diameter ratio 3.1 : 1. The direct Coombs test was now

strongly positive. The biopsy showed Hodgkin's disease of typical morphology.

Further transfusions were given, the blood being cross-matched in saline and albumin. There was considerable general improvement, and the patient was discharged on October 21 free from jaundice but still anaemic.

Comment.—This case illustrates the rather more common association of a haemolytic anaemia with Hodgkin's disease. The development of anaemia occurred during the first relapse two years after the initial attack and deep *x*-ray therapy. It is of interest that the haemolytic picture was fully developed before the Coombs test became positive. There is no reason to suppose that this finding was in any way related to the earlier transfusions, and it can be accepted as evidence of the activity of an immune haemolysin.

Case 4

An unmarried woman aged 66 had been in good health until one year previous to admission. She then noticed a tendency to bruise easily, and transient purpuric eruptions appeared. In April, 1949, she had acute pain in the left hypochondrium lasting two to three days. This recurred six weeks later. Some pain had persisted during the intervening seven months, and there was complaint of increasing lassitude.

She was admitted to hospital on February 3, 1950. The only abnormalities on physical examination were pallor and enlargement of the spleen, which was tender, the lower border being palpable below the umbilicus.

Investigation showed anaemia; haemoglobin, 32% (4.99 g.); red cells, 2,400,000. The film appearances did not suggest spherocytosis, but there was pronounced polychromasia with many stippled cells, reticulocytes 15%, and many late normoblasts. The red-cell fragility was slightly increased: haemolysis started at 0.55% saline and was complete at 0.30%. The direct Coombs test was positive.

The picture was typical of an acute haemolytic anaemia. As the course appeared to be progressive, and the cause was uncertain, the only hopeful line of treatment seemed to be splenectomy. This was performed on March 21. The operation was without unusual incident. After twenty-four hours, however, the anaemia increased rapidly and death occurred on March 24.

Post-mortem Findings.—Significant changes were confined to the reticulo-endothelial system. The liver was large, soft, pale, and without evidence of fibrosis. All the lymph nodes showed a slight fleshy enlargement. Microscopically the spleen (removed at operation) was congested but very cellular. Lymph follicles were present, showing central hyperplasia. The pulp was filled by histiocytic proliferation, many of these cells showing erythrophagocytic activity. In addition there were fairly numerous giant cells with bizarre and contorted nuclei (Figs. 1 and 2, Special Plate). Stained for iron, the sections showed a marked excess, both intracellular and extracellular, but none was present in the giant cells. The lymph nodes were very similar on section; and the same unusual type of giant cell was found in relation to the sinusoids in the liver. The marrow contained many histiocytes and giant cells, and was apparently devoid of erythropoietic tissue.

Comment.—This was a characteristic acute haemolytic anaemia associated with a widespread lymphadenopathy revealed only at necropsy. The histology was not characteristic of any of the commoner reticuloses. It was therefore considered whether the histological picture represented reactive changes in the reticulo-endothelial system such as may occur with prolonged haemolysis (Gittins, 1933; Davidson and Fullerton, 1938; Israëls and Wilkinson, 1938; Dyke and Young, 1938). Dameshek and Schwartz (1940), reviewing this subject, stated that of 29 cases of idiopathic acute haemolytic anaemia 12 showed histiocytic proliferation, often with giant-cell formation and erythrophagocytosis and ectopic marrow activity. The histological picture in Case 4 is in keeping with these descriptions, although no foci of myeloid metaplasia were seen. Nevertheless the bizarre nature of the giant cells, and the fact that they themselves showed no phagocytic activity or intracellular iron deposition, suggested disordered growth of neoplastic type. Considered, therefore, as a primary reticulosis, the picture closely resembles that of histiocytic medullary reticulosis (Scott and Robb-Smith, 1939). There are some points of difference. First, in life there was no clinical enlargement of the lymphatic nodes in this case, and even at necropsy the enlargement was not remarkable. Secondly, the clinical course of one year is longer than that recorded in histiocytic medullary reticulosis, the longest in the series quoted above being 32 weeks. Nevertheless, it is considered that the lymphadenopathy here is a primary reticulosis and falls into the group of histiocytic medullary reticulosis.

Discussion

The Type of Anaemia

Loutit and Mollison (1946), writing of the distinction between the congenital and acquired forms of haemolytic anaemia, list the known general causes of haemolytic anaemia as: (i) congenital defects of the erythron, (ii) bloodstream infections, (iii) exogenous toxins, and (iv) endogenous antibodies leading to red-cell destruction. Dameshek and his colleagues speak of idiopathic and symptomatic acute haemolytic anaemias which clearly belong to the fourth group above. In many such symptomatic cases the basic pathology is malignant disease.

Essential features of this type of anaemia are spherocytosis and increased fragility of the red cells. These two features are directly related, and have been shown to result from the exposure of normal cells to immune haemolytic serum (Dameshek and Miller, 1943). An inactive or aplastic state of the marrow heralds haemolytic crises (Owren, 1948; Dameshek and Bloom, 1948). In Case 4, in which the terminal stage of the disease was rapid and progressive, the marrow was aplastic at necropsy. Usually a normoblastic or macronormoblastic response follows (Cases 1 and 2). Thus when the patient is first seen the peripheral blood picture is often regenerative (Cases 1, 3, and 4). At such times, owing to the large number of young red cells in circulation, the fragility is often either slightly increased or within normal limits, and the spherocytic appearances may be masked. Evidence of the action of an immune-body haemolysin is usually found in these cases. A positive direct Coombs test is so interpreted. Recent figures of the incidence of such positive tests, and of haemolysin tests on the patient's serum using trypsinized red cells, showed 83% of acquired haemolytic anaemias, 32% of hereditary types (familial acholuric jaundice), and 27% of thrombocytopenic purpuras (Wright *et al.*, 1951). These tests are therefore of limited diagnostic value, although their development has led to important new views of pathogenesis.

Haemolytic Mechanisms in Malignant Disease

Three mechanisms capable of producing haemolytic anaemia seem possible in malignant disease of the types recorded here. First, infiltration of the bone marrow may cause some maturation abnormality, resulting in increased fragility. Secondly, the changes may be due to a circulating haemolysin. Thirdly, red-cell destruction can result from abnormal erythrophagocytosis.

The early appearance of haemolytic signs in two of the present cases (Cases 1 and 2) suggest that extensive marrow involvement is an unlikely cause; and this is supported by the case of Singer and Dameshek (1941) in which haemolytic anaemia was associated with a localized ovarian tumour and complete recovery followed removal of the tumour. Furthermore, the process by which marrow disturbance could result in spherocytosis is difficult to understand.

The frequency of positive haemolysin tests has already been referred to. The interpretation of these tests is somewhat speculative, but, taking them to indicate the sensitiza-

tion of red cells as a result of adsorption of antibody, it may be argued that the antibody in these cases is some product of the malignant tissue, or of reaction to this tissue.

Alternatively, the abnormal tissues may destroy excessive numbers of red cells, and thus provoke haemolytic antibody production. Whether this is the first step may depend on the type of reticulosis. Erythrophagocytosis is a usual and pronounced feature of histiocytic medullary reticulosis and an occasional finding in Hodgkin's disease; it occurs rarely if ever in significant degree in lymphosarcoma, while in carcinomatosis the abnormal cells have no phagocytic ability. In the last-named types, therefore, some factor other than phagocytosis must initiate the haemolytic process. The early appearance of haemolytic signs is also more readily understood on the basis of an antibody mechanism.

Summary

Four cases of haemolytic anaemia are described. They were associated with different types of reticulosis.

The type of anaemia and possible mechanisms of haemolysis are discussed.

I wish to thank the physicians of Guy's Hospital, under whom these patients were admitted, for the use of the case histories. Mr. E. S. Bolton, of Yeovil, and Dr. A. M. Thomas, of Taunton, gave generous help in the follow-up of Case 2. Dr. K. S. Rodan, of Shoreham-by-Sea, kindly supplied a section of the biopsy from Case 3. I am greatly indebted to Dr. C. W. Shuttleworth for the photomicrographs.

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On June 19 Tiverton and District Hospital celebrated its centenary. It was first opened as a dispensary for out-patients and intended for the relief of the sick poor. In 1865 additional wards were built and the whole converted into an infirmary for accident cases. The infirmary received its first in-patient in 1868. A children's ward of four cots, an isolation-room, and additional rooms for out-patients and nursing staff were added in May, 1892. In commemoration of Queen Victoria's diamond jubilee £1,700 was collected and spent on pay-wards for private patients and a new operating-theatre. Further gifts of land and money made it possible for more extensions and improvements. In 1932 Sir John Amory presented the hospital with a portion of the site, until then occupied by brewery premises. These were demolished and an extension built at a cost of £6,500, comprising a new kitchen, staff quarters, and other improvements. This was completed and brought into use in 1933. Finally, in 1947 the remainder of the old brewery premises was purchased and the accommodation for nursing staff enlarged. When the National Health Service started the hospital was placed under the authority of the Exeter and Mid-Devon Hospital Management Committee. It has 50 beds, of which four are for private or semi-private patients, and also a nursery with 11 cots. Since its foundation the work of the hospital has increased enormously. During the first 16 years of its existence 7,090 out-patients were treated, while during the year 1951 alone 5,595 out-patients were treated, involving a total of 14,847 attendances. There were also 1,703 in-patients admitted during the year, while the maternity department dealt with 241 births.

UNUSUAL FEATURES IN A FATAL CASE OF INFECTIOUS MONONUCLEOSIS

BY

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[WITH SPECIAL PLATE]

Infectious mononucleosis is generally recognized to be an acute infectious disease characterized by enlargement of the lymphatic glands, changes in the blood cells, especially mononucleosis, and a uniformly favourable course (Tidy, 1945). Fatalities from the disease have been rare. Bernstein (1940), in a comprehensive paper, stated that no one has ever died of uncomplicated infectious mononucleosis, and maintained that most of the fatal cases that have been reported were probably not examples of infectious mononucleosis at all, but rather of generalized sepsis with general gland enlargement. Of the fatalities dealt with in his survey some occurred from associated pulmonary disease (bronchopneumonia and empyema) and one from asphyxia following a ruptured retropharyngeal abscess. In another case a "delicate child" died while convalescing from scarlet fever (no further details are given).

Lassen and Thomsen (1940) recorded a mortality of about 1% in 500 cases admitted to the Blegdam Hospital. They reported two fatal cases due to degenerative processes in the central nervous system, localized apparently selectively to the respiratory centre and thus producing a central respiratory failure. Ziegler (1944) and Smith and Custer (1946) recorded fatal cases due to rupture of the spleen; the latter authors also reported deaths due to nasopharyngeal haemorrhage and laryngeal oedema (Custer and Smith, 1948). Two fatal cases presented as the Guillain–Barré syndrome (Ricker, Blumberg, Peters, and Widerman, 1947). Jersild (1942) performed a necropsy on a patient who died of myocarditis attributed to infectious mononucleosis. So far as we know there have been no reported fatalities from infectious mononucleosis which have been associated with severe jaundice and renal failure.

That liver-cell damage may be a cause of clinical jaundice in infectious mononucleosis was first demonstrated in 1942, when a liver punch biopsy showed focal acute hepatitis, and it was further observed that there was a rough correlation between the severity of the disease and the degree of hepatic impairment (Kilham and Steigman, 1942). However, as early as 1928 it was realized that liver changes, apart from those consequent upon obstruction from enlarged glands at the porta hepatis, occurred in glandular fever. It is now thought that some hepatocellular damage occurs in all cases of infectious mononucleosis, including those which exhibit no overt jaundice. Cohn and Lidman (1946) have described 15 cases without jaundice but all showing impairment of liver function as demonstrated by more than one chemical test. Hall (personal communication), in Liverpool, followed 12 cases with liver biopsies, but actual

necrosis of liver cells similar to that observed in infective hepatitis was not seen, although the possibility of permanent liver damage was discussed.

The incidence of nephritis in glandular fever is said by various authors to be up to 6%. Bernstein states that oliguria is exceptional and that there is neither oedema nor nitrogen retention. Renal function remains unimpaired, the course is benign, and recovery is rapid and invariable. He goes on to speculate that increased capillary permeability of the renal capillaries, which, as in anaphylactic purpura, could account for the urinary abnormalities, is merely a manifestation of the haemorrhagic diathesis that is not infrequently associated with glandular fever. Wechsler *et al.* (1946), in a study of 556 cases seen during an epidemic, reported abnormal urinary findings in 17 cases. The abnormal constituents were red and white blood cells, albumin, and hyaline and granular casts. The same uniformly benign course with rapid return to normal was noticed. Custer and Smith stated that the renal lesion of infectious mononucleosis is essentially an interstitial nephritis.

The purpose of reporting the following case is to show that, contrary to present conceptions, the hepato-cellular and renal damage in infectious mononucleosis may be associated with a fatal termination.

Case Record

A male art student aged 23 was admitted to the Rush Green Hospital on November 24, 1950. For the three weeks before admission he had complained of feverishness, especially in the afternoons, often accompanied by rigors and sweats. For the preceding 10 days he had suffered from a sore throat, arthralgia, headache, photophobia, nausea, anorexia, and constipation. The day before admission a rash had appeared on his abdomen and he had become jaundiced. On specific interrogation he admitted that his urine was "a dark-red colour" and his stools were "beige." He also affirmed that he had had some upper abdominal discomfort during the past few days. He had previously had excellent health apart from a mild paratyphoid B infection, contracted whilst in France, for which he was admitted to this hospital fourteen months previously. At that time the organism was isolated from the stools, and the Widal test was positive.

Examination showed that he was of excellent physique, though jaundiced and looking ill. His temperature was 102.8° F. (39.3° C.) and pulse rate 88. A red macular rash was present on the trunk and to a less extent on the arms, where it was mainly papular. There were no abnormalities in the cardiovascular and respiratory systems. The fundi were normal, Kernig's sign was negative, neck rigidity was not present, and the remainder of the central nervous system was intact. The liver and spleen were not palpable and were not enlarged to percussion. Several mobile enlarged glands, firm and not tender, were palpable in both groins and well above the inguinal ligament on the right side. There were similar glands in both axillae and the lateral chest wall on the left side. There was a large mass of glands in the anterior cervical triangle and submandibular area on the right side, and similar glands were present in the neck on the left side. The tonsils were enlarged and covered with exudate, which also spread on to the posterior pharyngeal wall. There was very little fetor oris. A provisional diagnosis of glandular fever was made, and in view of the history of dark urine and beige-coloured stools an obstructive lesion in the form of enlarged glands in the porta hepatis was postulated.

For the next three days he remained ill with a high continuous fever (103° F.—39.4° C.—although his pulse rate never rose proportionally), a slight increase in his jaundice, and biliuria. This biliuria persisted throughout his illness, although the loose stools which he passed contained bile.

On the fourth day "aureomycin" was given, and for the next two days there was some remission in the temperature and slight amelioration of symptoms; the lips, however, became tense and swollen at this time, but the swelling subsided in a few days. The concentrating power of the kidneys began to fail, as evidenced by the early morning specific gravity, which became fixed at 1010.

On the seventh day some fresh tender papular lesions appeared on the chest and back and the temperature was again raised; penicillin, 250,000 units four-hourly, was now given. He began to vomit brownish fluid and the spleen became palpable, although the superficial lymph nodes had been regressing in size.

On the eighth day the liver edge was palpable one finger-breadth below the right costal margin. On the ninth day the jaundice deepened to a golden bronze and the patient began to hiccup. The urinary output had fallen despite attempts to restore fluid loss, and the blood urea was 210 mg. per 100 ml. On the twelfth day the patient became frankly delirious, this condition alternating with periods of lethargy and semi-coma. Large quantities of brown fluid containing reduced blood were vomited and passed per rectum. His respirations had become deep and slow. The presence of free fluid in the peritoneal cavity was suspected.

In view of the rather sudden change in his mental condition—that is, the alternating coma and delirium, the persistent vomiting, the deepening jaundice, the haemorrhage from mucous membranes, and the fact that his liver, palpable the previous day, could no longer be felt—a provisional diagnosis of acute hepatic failure was made and the "intravenous liver regime" was begun—10% dextrose in normal saline with vitamin supplements. However, he failed to rally, and died on the thirteenth day.

Laboratory Investigations

1st Day.—R.B.C., 4,300,000, no malaria parasites seen; Hb, 81%; W.B.C., 3,900 (polymorphs 10%, lymphocytes 80%, monocytes 2%, atypical monocytes 8%). Paul–Bunnell, 1:256 (antibody not adsorbed with guinea-pig kidney).

Widal test: *Salm. typhi* O, positive 1:50; *Salm. typhi* H, negative; *Salm. paratyphi B* O, positive 1:25; *Salm. paratyphi B* H, positive 1:250; non-specific salmonellae, positive 1:250. The Widal reaction on his previous admission (September 27, 1949) is given for comparison: *Salm. typhi* O, negative; *Salm. typhi* H, negative; *Salm. paratyphi B* O, negative; *Salm. paratyphi B* H, positive 1:250+; non-specific salmonellae, positive 1:125. Throat swab, heavy growth of coagulase-positive *Staphylococcus aureus*. Stools, no pathogens present. Chest *x*-ray film N.A.D.

2nd Day.—Paul–Bunnell, 1:256 (antibody not adsorbed with guinea-pig kidney).

3rd Day.—Mid-stream specimen of urine: bile ++; albumin ++; large number of granular casts, with a few red cells, white cells, and renal cells; culture sterile.

4th Day.—Blood culture, sterile aerobically and anaerobically.

5th Day.—W.B.C., 3,600 (polymorphs 43%, lymphocytes 36%, monocytes 1%, atypical monocytes 20%). Mid-stream specimen of urine: albumin +; bile +; occasional red cells. Paul–Bunnell unchanged.

8th Day.—W.B.C., 5,400 (polymorphs 52%, lymphocytes 27%, monocytes 8%, eosinophils 2%, atypical monocytes 11%); van den Bergh, biphasic reaction; serum bilirubin, 24 mg. per 100 ml.; serum alkaline phosphatase, 60 (King-Armstrong) units.

10th Day.—Stools still negative for paratyphoid and other pathogens. Blood urea, 100 mg. per 100 ml.

11th Day.—Blood urea, 210 mg. per 100 ml.

12th Day.—Blood urea, approximately 300 mg. per 100 ml.

Post-mortem Examination Within Twelve Hours of Death

The body was that of a well-built young man. The skin was deeply and uniformly icteric. *Head and Neck:* Swelling of the lips, otherwise nothing abnormal. No cervical glands seen and throat quite clear. *Chest:* Both pleural sacs contained clear bile-stained fluid. No adhesions present. *Heart:* Pericardial effusion, bile-stained. Otherwise heart muscle, valves, and vessels appeared normal. *Lungs:* Healthy, and no enlarged lymph nodes found in the thorax. *Abdomen:* Large collection of bile-stained ascitic fluid. *Stomach:* Large and empty. *Gut:* General distension, the lower ileum containing altered blood and mucus. The coeliac glands were enlarged, pinkish, and of a rubbery consistency, and matted together, though easily separated. *Liver:* Slightly enlarged (not weighed) and gave a gross appearance of subacute yellow atrophy (hepatitis). Regular and diffuse yellow and pinkish mottling throughout the organ. The hilar glands were large, rubbery, and oedematous, resembling those of the coeliac group. No apparent abnormality of the gall-bladder noted, nor any obstruction of the bile ducts. *Spleen:* Enlarged to about four times normal (not weighed), with a well-marked anterior notch. Smooth and regular, with a tense capsule. Pulp firm and dark in colour with diffuse mottling. No infarcts. *Pancreas:* No gross abnormality. *Kidneys:* Both showed engorgement and moderate cloudy swelling. *Adrenals:* Nothing abnormal noted.

Permission for examination of the central nervous system was refused.

No other important features were seen. Histological sections were made from the liver, coeliac glands, spleen, and kidney (haematoxylin and eosin, Leishman, and iron-staining).

Histological Reports

Hilar gland (Fig. 1, Special Plate) shows follicular and sinus infiltration with numerous lymphocytic cells, many of which are primitive ? lymphoblasts. Some possess irregular mottled nuclei and resemble the abnormal "monocytes" of the blood. Giant cells and macrophages are fairly numerous, and some contain regular granular yellowish pigment. Most of this gives a negative Perles reaction for iron, though some irregular haemosiderin deposits are present in the stroma. Patchy oedema with capillary engorgement and haemorrhages are seen in the medulla, besides the "monocytic" infiltration. Some sinus reticulosis is also present.

Liver (Fig. 2).—Moderate perilobular fibrosis. Infiltration, most pronounced in the periportal areas, but also pericellularly, with lymphocytes and ? abnormal monocytic cells, and a few giant cells. Suggestive of leukaemic picture, but the cells are less uniform and show irregularities in the shape and staining of the nuclei. The liver cells show some cloudy swelling. Areas of necrosis are a noteworthy feature, though this is not extensive in degree. Hyperplasia and regeneration are both seen, but are not pronounced.

Spleen (Fig. 3).—General engorgement; capillary haemorrhages and granulations under the rather thin capsule. Numerous pigment-containing macrophages. Pulp and sinuses show numerous lymphocytic and atypical cells.

Kidney (Fig. 4).—Glomerular engorgement, but little other change in the cortex. Tubular degeneration, with cloudy swelling, is general. Blood casts and a few granular casts seen. Medullary oedema and intertubular collections of cells similar to those seen in the lymph nodes.

Discussion

It is submitted that the diagnosis of this case as infectious mononucleosis is valid, as it satisfies the accepted criteria—namely, the clinical presentation, the presence of atypical monocytes up to 20% in the peripheral blood, the presence of heterophil agglutinins in a titre over 1:128, the agglutinins not being adsorbed by guinea-pig's kidney, and the existence of the infectious mononucleosis cells in necropsy material. The unusual features are: (1) the degree of hepatic impairment as observed clinically and the finding of necrosis of liver cells on post-mortem examination; (2) the degree of renal impairment; and (3) the fatal outcome.

It may be argued that in view of the high serum bilirubin and raised serum alkaline phosphatase and the necropsy finding of the enlarged glands in the porta hepatis, the jaundice was solely obstructive in nature. Cohn and Lidman (1946) have noted the serum alkaline phosphatase to be abnormally high in those cases of infectious mononucleosis even without clinical jaundice. It must be remembered that while the patient observed his stools to be "beige-coloured" before admission, all specimens examined whilst he was in hospital (including those examined in the laboratory for paratyphoid) contained bile pigment. The explanation of this is probably that the enlarged glands in the porta hepatis which were found at necropsy were of a size sufficient to have caused bile-duct obstruction at a time before his admission, but they later, in company with the superficial lymph nodes, subsided. Bile pigment was obvious in all urinary specimens, but bilirubinuria was the rule in all the cases investigated by Cohn and Lidman (1946) although they had a normal serum bilirubin. Our patient's van den Bergh reaction was biphasic, for what it is worth. Notwithstanding all this the clinical picture was rather more severe than the actual hepatic damage would suggest.

The nature of the lesion causing the uraemia is more conjectural. At first we postulated a "cholaemic nephrosis." This condition is often present in diseases characterized by jaundice and liver failure; the kidneys are found to be swollen and the epithelium of the convoluted tubules shows a variable but often considerable degree of necrosis, which is rapidly followed by regeneration. It is supposed that the necrotic process is due to toxic substances absorbed from the bowel which the severely damaged liver has failed to destroy. In the series investigated by Lucké (1944), however, liver damage was described as acute massive necrosis.

Doubtless extrarenal factors—continued fever, vomiting, and the alimentary tract haemorrhage—contributed to the azotaemia, despite measures adopted to offset these. These factors nevertheless do not explain fully the renal pathology found. In addition it is to be noted that failure of concentrating power, albumin, blood, and granular casts appeared in the urine before the extrarenal factors (except fever) were operative. One is left, therefore, with the speculation whether the "infiltration" with normal and abnormal lymphocytic and monocytic cells has caused the renal damage and subsequent failure.

Summary

A brief review of the nature of the fatal cases of infectious mononucleosis in the literature has been made, with special reference to the hepatic and renal changes.

A fatal case is recorded in which death was due to liver and kidney failure and in which there were more pronounced pathological changes in these organs than have previously been noted.

We are very grateful to Dr. E. James, medical superintendent of Rush Green Hospital, for permission to publish, and for his help and interest in connexion with this case. We should also like to thank Dr. R. J. Cureton, of the Department of Pathology of St. Bartholomew's Hospital, for his assistance, and Dr. Sansom, who prepared the photomicrographs.

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DUPUYTREN'S CONTRACTURE TREATED WITH VITAMIN E

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[WITH SPECIAL PLATE]

Dupuytren's contracture is a self-limiting condition. The stage at which arrest occurs varies from a slight thickening of the palmar fascia to marked thickening with extreme flexion deformity of one or more digits. It is therefore essential, when considering the effect of any treatment, to remember the possibility that the condition may have become quiescent.

A number of investigators have written about the treatment of this condition with vitamin E, and the results have been contradictory. None of these investigators have mentioned whether the vitamin E was the sole method of treatment in their series of cases or whether it was associated with massage, active or passive stretching, wax baths, night splints, etc.

As previously mentioned, some cases progress no further than the stage of slight thickening of the palmar fascia, while others can be controlled by the above-mentioned physiotherapeutic measures, and, indeed, slight flexion deformity of the fingers can occasionally be diminished by this means.

In the present series of cases vitamin E was the only form of treatment. Tocopherol acetate ("ephynal"), 100 mg. twice daily, was administered orally for a minimum period of three months. This dosage and the period of administration seemed reasonable for the purpose of producing a response, should any be likely to occur. On this dosage no toxic effects were noted. All cases were followed up for a minimum period of three months and the majority for one year after discontinuation of the vitamin E. Of 46 patients treated, 24 had bilateral lesions, so that 70 hands were involved. The cases were divided into three groups.

Group I.—This group comprised 48 hands in which there was a thickening of the palmar fascia only. In assessing the results in this group I had to rely on my own observations and those of the patients. In no patient was any improvement observed. It is interesting to note that one patient had had swelling, softening, pain, and tenderness in the thickened fascia a few months before the beginning of treatment, but nothing of this nature had occurred during treatment. Another patient had similar symptoms both before and during treatment.

Group II.—Here there was a thickening of the palmar fascia with a flexion deformity of one or more digits, but this was not greater than 30 degrees at either the metacarpo-phalangeal or the interphalangeal joints. There were 15 hands in this group, and a plaster-of-Paris cast was made of the deformity in each case before the onset of treatment. By this method it was possible to demonstrate whether any change had occurred. In no case was there any improvement, and in three cases the deformity had increased. One patient thought the deformity had decreased, but the plaster cast failed to confirm this. Another lost the softening, pain, and tenderness which had been present, while a third had experienced these symptoms some time before treatment was begun. In this type of case it is sometimes possible to diminish or even abolish the flexion deformity of the digits by the continuous application of physiotherapeutic methods.

Group III.—In these cases there was thickening of the palmar fascia with flexion deformity of one or more digits greater than 30 degrees at the metacarpo-phalangeal or interphalangeal joints. Nearly all these cases had the fingers flexed well into the palm and one had extension at the terminal interphalangeal joint. There were seven hands in this group, and a cast was made of each deformity. There was no improvement in any case, while three became definitely worse. One patient thought the deformity was less, but the cast proved otherwise.

Post-operative cases have not been treated, as the operative technique employed is one of complete removal of the palmar fascia, including the extensions into the affected fingers and the vertical septa going down to the metacarpals. After this complete removal there is, in my experience, no tendency to recurrence.

Discussion

The ages of these patients varied from the middle twenties to the early eighties, while the duration of the condition varied from a few months to 30 years. Patients are vague with regard to the duration of the condition as a rule, so that the time given by most of them is an approximate one. Therefore, so far as is possible, all stages in the development of the condition have been included.

I have endeavoured to remove the element of human error by the employment of plaster casts in estimating the degree of deformity. In the first group, however, where this was not applicable, reliance had to be placed on my own observations and those of the patients.

Pain, tenderness, and swelling in the palmar fascia has been suggested by Thomson (1949) as an indication of a specific response. These symptoms were experienced by four of our patients before the administration of vitamin E; they can therefore hardly constitute a specific response to the action of the vitamin. I have noticed these features previously in cases of Dupuytren's contracture, and regard them rather as unfavourable milestones in the progress of the condition. The tender, painful, swollen areas in the palmar fascia are composed of young fibrous tissue which later develops into the dense avascular collagenous tissue of the contracture. (See Special Plate for photomicrographs.)

Summary

A series of 46 cases of Dupuytren's contracture were treated; 24 had bilateral lesions. The patients were divided into three groups according to the degree of the deformity. Vitamin E was the sole form of treatment, and in no case was any improvement noted.

I should like to thank Professor Dorothy Russell and her staff for the pathological sections and Mr. King for the photomicrographs.

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West Africa (May 24) reports that Dr. W. S. S. Ladell, of the Hot Climate Physiological Research Unit, Oshodi, told a recent conference on desert research that he disapproved of the practice of taking a siesta in hot countries. Opposition to it was based on physiological grounds, and was one of the conclusions reached by workers at the unit after widespread investigation into the capacities of men from temperate climates and of Nigerians for work in tropical heat. These investigations are still in progress, but Dr. Ladell has already been able to make certain generalizations. One of these is that, unless he has been specially trained, the Nigerian worker is not much more tolerant of severe conditions of heat than other workers.

UNDESIRABLE SIDE-EFFECTS FROM DECAMETHONIUM IODIDE

BY

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Decamethonium iodide (C10) is a cheap and easily prepared compound. The short duration of muscular relaxation which it produces and the apparent absence of undesirable side-effects (Hewer *et al.*, 1949; Organe, 1949; Davies and Lewis, 1949; Bailey and Murphy, 1951) led us to suppose that this drug could be employed usefully in surgical procedures requiring relaxation for short periods. It was also used in repeated doses to produce relaxation for longer periods.

Present Investigation

In a series of 233 administrations of C10 to subjects between the ages of 16 and 75 (see Table) we have noted one case of cumulative action similar to those reported by Gray (1950) and Barry *et al.* (1951). We also had four cases which exhibited cardiovascular abnormalities.

Analysis of 233 Administrations of C10

Operation	No. of Cases
Appendicectomy	67
Hysterectomy and gynaecological operations	25
Herniorrhaphy	49
Urogenital operations	26
Haemorrhoidectomy	23
For perforated peptic ulcer	8
Exploratory laparotomy	5
Operations on the stomach	7
Operations on the bowel	8
Oesophagoscopy	4
For laryngeal spasm	11

The antidote to C10 is pentamethonium iodide (C5). A fall in blood pressure follows the intravenous injection of the antidote. It is stated that this reaction is likely to be severe in hypertensive or anaesthetized subjects (Enderby, 1950; Davison, 1950). This has been held to be one of the disadvantages of C10 compared with D-tubocurarine and gallamine triethiodide, the antidote to the latter drugs being neostigmine. It has now been suggested that the use of neostigmine in certain cases is not without danger. Neostigmine is given with atropine intravenously, the atropine to prevent excessive bronchial secretion which may be produced by the neostigmine. Deaths have been reported following the simultaneous intravenous injection of atropine and neostigmine (Macintosh, 1949; Clutton-Brock, 1949). Electrocardiographic recordings taken during anaesthesia have shown that ventricular arrhythmias and ventricular tachycardia have occurred after the intravenous injection of atropine in subjects who have increased carbon dioxide tension (Johnstone, 1951). A subject may be in this condition if he has not recovered from the intercostal paralysis produced by a relaxant drug. Johnstone also states that the intravenous injection of neostigmine may in some cases cause ventricular tachycardia. He suggests that these factors may have caused death in the cases reported by Macintosh and Clutton-Brock. We believe that in our present state of knowledge the antidote should not influence the choice of relaxant drug. Assisted respiration should be maintained, with an endotracheal tube *in situ*, until respiratory excursions are adequate, if there is any residual intercostal paralysis after the administration of a relaxant drug.

"Syncurine" brand of C10 was used: a test dose was not given. Paton and Zaimis (1950) state that circulating adrenaline antagonizes the action of C10, and that misleading results will be obtained by administering this drug to unanaesthetized and apprehensive subjects. Anaesthesia was induced with thiopentone in all cases. An initial dose of 3 mg. of C10 was given, either immediately after induction to facilitate intubation or about five minutes before relaxation was required by the surgeon. Anaesthesia was maintained with cyclopropane and oxygen; minimal ether and oxygen; gas, oxygen, and "trilene"; or intermittent thiopentone, gas, and oxygen. It was sometimes necessary to give a further 2 or 3 mg. of C10 if relaxation produced by the initial dose was inadequate. We found that subjects of the same build and having similar muscular development varied in their response to the initial dose. Some showed no obvious alteration in respiratory excursions and inadequate relaxation. Others exhibited varying degrees of intercostal paralysis which lasted from five to fifteen minutes. The return of muscle tone was rapid and unpredictable, a source of embarrassment to the surgeon and anaesthetist.

Recent work on the mode of action of relaxants (Paton and Zaimis, 1950) explains why it is not easy to compare the effects of C10 and D-tubocurarine. The former drug has a similar action to that of acetylcholine, the muscle end-plate is depolarized and a neuromuscular block produced (Burns and Paton, 1950). D-tubocurarine is said to raise the threshold of the motor end-plate to acetylcholine. Factors present during anaesthesia differ in their effects on the relaxation produced by the two relaxant drugs. For example, ether slightly antagonizes C10, but a synergistic effect is seen with D-tubocurarine with a resulting increase in paralysis produced. The presence of circulating adrenaline increases the stimulant effect of C10 and decreases the maximum paralysis. The opposite effect occurs with D-tubocurarine.

We found that C10 facilitated oral intubation and relaxed a laryngeal spasm enough to permit the passage of an endotracheal tube. It was also used in subjects who were heavy cigarette smokers. After induction with thiopentone, the coughing and spasm encountered during the transition from thiopentone to ether or trilene could be avoided.

Case 1

A small man aged 65 with chronic bronchitis and occasional extrasystoles was operated on for rectal prolapse. His blood pressure was 160/80. Premedication with morphine, 1/6 gr. (11 mg.), and atropine, 1/100 gr. (0.65 mg.), was given 45 minutes before operation. Anaesthesia was induced with 0.2 g. of thiopentone and maintained with cyclopropane, oxygen, and minimal ether. Enough relaxation of short duration for oral intubation to be performed was produced by 3 mg. of C10 injected intravenously. Two further doses of 2 and 3 mg. were given, the final one 30 minutes after induction of anaesthesia. Intercostal paralysis was produced but not apnoea. The operation was completed 45 minutes after the final dose of C10 was given. The respiration was shallow and diaphragmatic only, and there was marked tracheal tug. Cyanosis could be avoided only by rhythmic inflation of the lungs with oxygen. One hour later respiratory excursions were greater and there was no cyanosis when breathing air unassisted. Some intercostal paralysis and tracheal tug still persisted. The patient was now semi-conscious and his general condition was satisfactory. He was returned to the ward with the endotracheal tube *in situ* and oxygen was administered through a B.L.B. mask; 45 minutes later he coughed out the tube. He was now fully conscious, the respiratory excursions had returned to normal, and there was no residual paralysis. Postoperatively there was some exacerbation of his bronchitis. The sputum was expectorated easily and improvement rapidly occurred.

Case 2

A man aged 53, in good general condition, was operated on for repair of a ventral hernia. Premedication was with "omnopon," ¼ gr. (22 mg.), and hyoscine, 1/150 gr.

(0.43 mg.), given two hours before operation. The nasal cavities were sprayed with 10% cocaine, and anaesthesia was induced with 0.4 g. of thiopentone, nitrous oxide, oxygen, and trilene. Blind nasal intubation was performed and maintenance continued with nitrous oxide and oxygen. A further 0.2 g. of thiopentone was given in fractional doses, some respiratory depression was produced, and respiration was assisted. Respiratory excursions were adequate when the first incision was made. When 3 mg. of C10 was injected intravenously there was an immediate onset of paroxysmal tachycardia, the pulse being uncountable and grossly irregular. The tachycardia lasted a few seconds only, the arrhythmia about two minutes. During this time there was a fall in blood pressure. The pulse rate then fell to 58 and returned to normal in a few minutes. As the 3 mg. of C10 did not produce adequate relaxation vinesthene–ether mixture was added. An electrocardiogram taken half an hour after the onset of the cardiovascular disturbance showed no abnormality. The general condition, blood pressure, and pulse rate remained satisfactory during the rest of the operation, and the post-operative progress was uneventful.

Case 3

An obese woman aged 53, in good general health, had a subtotal hysterectomy for uterine fibroids. Her blood pressure was 140/80. Premedication with morphine 1/6 gr. (11 mg.), and atropine 1/100 gr. (0.65 mg.), was given 45 minutes before operation. Anaesthesia was induced with 0.4 g. of thiopentone and maintained with cyclopropane and minimal ether. An orotracheal tube, lubricated with 10% cinchocaine hydrochloride ointment, was passed under direct vision. A pharyngeal pack was inserted to prevent gases being blown into the oesophagus should assisted respiration become necessary. The cyclopropane was turned off and anaesthesia maintained with oxygen and minimal ether. The blood pressure was now 120/80 and the pulse rate 80. The patient was placed in the Trendelenburg position and 3 mg. of C10 injected intravenously. Immediately after the injection the pulse rate dropped to 60 and she became pale. Ten minutes later the pulse rate was still 60 and the blood pressure 90/30. There were diminished respiratory excursions and relaxation was adequate. Respiration was assisted and there was no cyanosis. "Methedrine," 15 mg., was injected slowly intravenously and the same dose intramuscularly. In 10 minutes the blood pressure rose to 100/60 and the pulse rate to 70. Thirty minutes later the blood pressure was 120/70 and the pulse rate 90. Respiratory excursions were adequate and there was no tracheal tug. At the end of the operation there was no residual paralysis and the post-operative progress was satisfactory except for some vomiting on the first day.

Case 4

A thin man aged 48, in good general condition, was operated on for the removal of a ureteric calculus. His blood pressure was 130/80. Premedication with hyoscine, 1/150 gr. (0.43 g.), and potassium bromide and chloral, 30 gr. (2 g.) of each, was given two hours before operation. Anaesthesia was induced with 0.5 g. of thiopentone and continued as in Case 3. The patient was placed in the lateral position; the blood pressure was now 120/70 and the pulse rate 80, and 3 mg. of C10 was injected intravenously. Relaxation was inadequate and ten minutes later a further 2 mg. was injected. The pulse rate fell at once to 50 and the blood pressure to 90 systolic. There was marked intercostal paralysis and tracheal tug; respiration was assisted. As methedrine had improved Case 3, it was injected as before. In 20 minutes the blood pressure rose to 140/80 and the pulse rate to 80. The respiratory excursions were now adequate. The operation was completed in 50 minutes and recovery from the anaesthetic was uneventful.

Case 5

This case of an obese woman aged 53 is included, though other factors present were capable of producing the cardiovascular irregularities. Her blood pressure was 210/100. The pulse rate was 80 and regular and there was no history of anginal attacks. The operation performed was a subtotal hysterectomy and the removal of a large ovarian cyst. Premedication with hyoscine, 1/150 gr. (0.43 g.), and potassium bromide and chloral, 20 gr. (1.3 g.) of each, was given two hours before operation. Anaesthesia was induced with 0.5 g. of thiopentone and continued as in Cases 3 and 4. The blood pressure was now 180/90 and the pulse rate 90 and regular in rhythm. The patient was placed in the Trendelenburg position and 3 mg. of C10 was injected intravenously. Fair muscular relaxation was obtained, the respiratory excursions were diminished, and respiration was assisted. Twenty minutes later the surgeon had great difficulty in delivering the cyst from the wound and more relaxation was asked for: 2 mg. of C10 was injected intravenously and at the same time the cyst was ruptured while attempts were being made to deliver it. The blood pressure fell to 100/40 and the pulse rate to 40. Respiration was assisted and 15 mg. of methedrine was injected slowly intravenously. A further 15 mg. was injected intramuscularly. In 30 minutes the blood pressure had risen to 200/100 and the pulse rate to 90. At the end of the operation the respiratory excursions were adequate and the general condition was satisfactory.

Comment

Some justifiable criticisms can be made of the dosage of C10 employed. In Case 1 a relatively large dose, 7 mg. in all, was given to a frail and elderly man with chronic bronchitis. Case 5 having received 3 mg. of C10, further relaxation should have been obtained by deepening anaesthesia. It is now our opinion that it is advisable to withhold relaxant drugs from elderly and obese subjects who are to be placed in the lateral or Trendelenburg positions. In the lateral position there is a 10 to 12% loss in vital capacity (Case and Stiles, 1946). With the Trendelenburg position the loss is 14 to 20% with 20 to 22.5 degrees of tilt (Altschule, 1943; Case and Stiles, 1946). In this position the bowels and omentum fall on the diaphragm or are pressed there by abdominal packs. The alterations in pulse rate and blood pressure occurred in subjects over 45 years of age, in all of whom an endotracheal tube had been passed.

In Case 5 the changes coincided with the rupture of an ovarian cyst and therefore a sudden decrease in intra-abdominal pressure in a hypertensive subject. These abnormalities all occurred at the moment of injection of C10. They could, however, be the result of irritation of the larynx and trachea in a light plane of anaesthesia by the endotracheal tube causing reflex vagal inhibition. It is also possible that the inhalation of too great a concentration of anaesthetic vapour, made easy by the presence of an endotracheal tube, may stimulate a pulmo-cardiac reflex. We have not encountered such abnormalities when using D-tubocurarine or gallamine triethiodide in similar circumstances.

Summary

Decamethonium iodide was administered to 233 subjects between the ages of 16 and 75.

The degree of muscular relaxation and respiratory paralysis was found to be variable when using a standard dose of 3 mg.

One case of cumulative effect and four showing cardiovascular abnormalities were encountered.

ADDENDUM.—Since writing this article we give atropine and neostigmine if there is some residual paralysis following the use of D-tubocurarine and gallamine triethiodide, but the drugs are not given simultaneously. The atropine is injected intravenously ten minutes before it is proposed to inject the neostigmine. If the pulse rate is slow and there is no rise in rate after the injection of atropine, neostigmine is not given.

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"NILODIN" IN TREATMENT OF SCHISTOSOMA HAEMATOBIUM

BY

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Owing to reports by various workers that "nilodin" brand 1-diethylaminoethylamino-4-methylthioxanthone hydrochloride, sometimes referred to in the literature as "miracil D," has a definite place in the treatment of bilharziasis (Blair *et al.*, 1947; Abdel Azim *et al.*, 1948), the following observations on seven cases of urinary *S. haematobium* treated with the drug may be useful. The number of cases is so small that no claim is made that the results are significant.

Case Reports

Case 1.—A Sudanese girl aged 12 was given 15 mg. of nilodin per kg. of body weight daily for five consecutive days. Her urine was examined daily and showed a large number of *S. haematobium* ova, red blood cells, and pus cells. Her initial weight was 35 kg., but she had lost about 6 kg. by the end of the five days' treatment. Her skin, sclerotics, mucous membranes, and urine were a deep yellow. Although her appetite was impaired she was not troubled by nausea or vomiting and she tolerated the drug fairly well. Ten days after the cessation of treatment the urine was still yellow, and, although the red cells and pus cells were fewer than before treatment, there were still viable ova. During an interval of a month without treatment viable ova were constantly present in the urine, but she regained her initial weight and lost the yellow coloration. A second course of 15 mg. per kg. of body weight daily for five days was given, and almost the same effects were encountered as during the first course. After another month's interval a third course was given. The urine still contained viable ova one month after the third course—that is, 105 days from the beginning of treatment.

Case 2.—A Sudanese man aged 23 was given 15 mg. of nilodin per kg. of body weight daily. He took the drug for two days and then developed a severe gastritis, which showed itself in the form of nausea and troublesome and continuous vomiting, together with a slight rise in temperature. He lost weight rapidly and looked toxic; the skin, sclerotics, and urine were yellow. After a lapse of about four months he was persuaded to undergo another course of treatment. This time, to soothe the mucous membrane of the stomach, he was put on a bismuth mixture two days before the beginning of treatment and also during treatment. He took the tablets for two days, but on the third day severe vomiting developed and he could not continue with the treatment. The urine contained a large number of viable ova two months after this attempt.

Case 3.—A Sudanese boy, aged 13 and weighing 40 kg., was given 15 mg. of nilodin per kg. of body weight for two days. He then developed severe and troublesome vomiting. Treatment was stopped on account of intolerance. His urine contained a large number of viable ova at the end of this treatment.

Case 4.—A Sudanese man aged 45 was given 15 mg. of nilodin per kg. of body weight (weight, 60 kg.). He took the drug for two days; it was then stopped on account of intolerance, as shown by severe and troublesome vomiting.

Case 5.—A Sudanese woman aged 53 was infected with *S. haematobium*. Her liver and spleen were not palpable. There were no urinary complications. Examination of the urine revealed red blood cells, pus cells, and a large number of ova. She was put on 15 mg. of nilodin per kg. of body weight (weight, 50 kg.). The tablets were spread over the day and given after meals. On the third day of treatment she lost her appetite and developed a yellow discoloration of the skin and conjunctivae. However, she continued treatment for five days, her urine still containing ova of *S. haematobium*. After a fortnight's rest a second course of 700 mg. of nilodin daily for five days was given. Sickness and yellow discoloration of the skin again ensued. Her urine still contained viable ova. A third course of 700 mg. daily for five days was given a fortnight later. This time she developed severe vomiting and profuse sweating, and lost 7 kg. in weight. Viable ova were still present in the urine 75 days from the beginning of treatment.

Case 6.—A Sudanese boy aged 15 who suffered from urinary *S. haematobium* was given 15 mg. of nilodin per kg. of body weight daily. On the third day he developed severe vomiting and yellow discoloration of the skin, conjunctivae, urine, and mucous membranes, and refused to continue treatment. He lost 3 kg. in weight. His urine still showed a large number of viable ova.

Case 7.—A Sudanese man aged 26 with urinary *S. haematobium* was given 15 mg. of nilodin per kg. of body weight. He contracted his disease five years before and had had two courses of antimony treatment without being cured. On the third day he developed vomiting and yellow discoloration of the skin, but continued the treatment until the fifth day. He lost 4 kg. in weight. His urine contained viable ova a fortnight from the beginning of treatment. He declined to have a second course of nilodin.

Discussion

The treatment of schistosomiasis with antimony tartrate, which was started some 35 years ago by Christopherson (1918) in the Sudan, is not entirely satisfactory. The therapeutic dose of antimony is not far removed from the toxic dose, and the relapse rate in treated cases is high. Another disadvantage of the drug is that it is given by the intravenous route. For all these reasons a new drug which can be taken by mouth is welcome. When nilodin became available I took the opportunity of trying it on cases of urinary *S. haematobium*.

Only one of the seven cases treated tolerated the drug fairly well. The other six showed signs of toxicity, usually on the third day. Yellow discoloration of the skin and mucous membranes, loss of appetite, vomiting, and rapid wasting were the predominant signs. The use of bismuth preparations did not help in decreasing the toxicity of nilodin. In most of the cases the intolerance was so great that it was not possible to complete the treatment. No case was cured. The patient who tolerated the drug was given three courses of treatment, but she continued to pass viable ova 105 days after the beginning of treatment.

From so small a number of cases no conclusions can be drawn regarding the therapeutic value of nilodin. The intolerance to the drug among Sudanese is in my opinion a deterrent to its use for mass treatment.

Summary

Seven cases of *S. haematobium* were treated with nilodin.

None of the seven cases was cured as the result of treatment.

The toxicity of the drug is a deterrent to its use in the mass treatment of *S. haematobium* in the Sudan.

I am indebted to Brigadier J. S. K. Boyd for the supplies of nilodin used in the cases here recorded; to Dr. R. Kirk for his help and encouragement; and to the Director, Medical Services, Ministry of Health, Sudan, for permission to publish these observations.

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SELF-EXPERIMENTS WITH SUCCINYLCHOLINE CHLORIDE

A NEW ULTRA-SHORT-ACTING MUSCLE RELAXANT

BY

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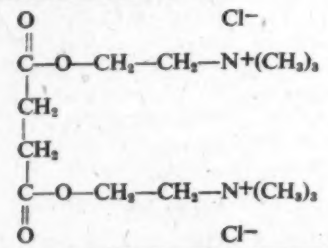
The purpose of this paper is to describe the action, in man, of a new synthetic muscle relaxant. Our tests were carried out with the aim of proving the safety and specific action of succinylcholine chloride (S.C.C.) as a short-acting curarizing agent for patients under anaesthesia.

With the muscle relaxants in use in clinical anaesthesia a more superficial plane of general anaesthesia can be maintained, to the benefit of the patient. The introduction of curare (Griffith and Johnson, 1942) was followed by the development of synthetic relaxing agents, the best known of which to-day are "flaxedil" (gallamine triethyliodide) (Bovet, Depierre, *et al.*, 1947, 1949; Mushin *et al.*, 1949) and decamethonium iodide or bromide ("eulissin," "syncurine," C10) (Paton and Zaimis, 1948, 1949; Organe, 1949; Vetten and Nicholson, 1950). The lack of sufficient controllability, the occasional prolonged curarization, and the more or less marked side-effects (release of histamine and blockade of the autonomic ganglia) are the main disadvantages of all the compounds mentioned, be their paralysing effect due to a true blockade at the neuromuscular junction, as with D-tubocurarine and flaxedil, or due to depolarization of the end-plate and its surrounding, as is the case with decamethonium (Alam *et al.*, 1939; Comroe and Dripps, 1946; Vetten and Nicholson, 1950; Burns and Paton, 1951).

Succinylcholine iodide (S.C.I.) was first described by Bovet, Bovet-Nitti, *et al.* (1949). Its strong paralysing power was recognized in animals, but no clinical tests were undertaken. Ginzel, Klupp, and Werner (1951a, 1951b, 1951c), at the Pharmacological Institute of Vienna University, examined thoroughly both S.C.I. and S.C.C.

The Properties of S.C.C.*

The chemical formula of S.C.C. is



Physical Properties.—S.C.C. is supplied (as dihydrate) in 5-ml. ampoules containing 20 mg. of the substance in 1 ml. The solution is stable and has frequently been kept for several weeks outside the refrigerator without any decomposition becoming apparent. It is miscible with solutions of thiopentone and also with pethidine. No decrease of the usual effect could be observed when the drug was used in any of these mixtures.

Pharmacology.—S.C.C. was tested in frogs, cats, pigeons, and dogs in comparison with other compounds with a similar chemical structure (Ginzel *et al.*, 1951a, 1951b, 1951c). The entire series showed nicotine-like stimulating effects as well as muscular paralysis. S.C.C. had the strongest neuromuscular blocking effect and the weakest stimulating action to the autonomic ganglia. In artificially ventilated cats some slight rise in blood pressure did not occur until doses as high as several hundred times the paralysing dose were being given. The paralysing effect on the skeletal muscle is due to the same mechanism as with decamethonium: depolarization of the end-plate region (Ginzel *et al.*, 1952). Its action, therefore, is not counteracted by anti-choline-esterases as is the case with D-tubocurarine and flaxedil. It may even be prolonged and intensified to some extent. There appears to be the same antagonism between S.C.C. and curare as has previously been described for decamethonium and curare (Paton and Zaimis, 1949). Since S.C.C. is probably broken up by enzymatic hydrolysis into the non-effective monocholine ester of succinic acid and free choline within a matter of minutes, no antidote is felt to be needed in clinical practice.

Methods and Dosage

From previous tests with other synthetic curarizing agents (Mayrhofer and Hassfurther, 1951) the fact was known that sensibility to these compounds varies widely between different animals and humans.

For the self-experiments on an unanaesthetized 30-year-old male (O. K. M.) of 176 lb. (80 kg.) body weight only the intravenous route was used. In the first three experiments the injections were given fast (within two seconds). The doses varied between 0.125 and 0.375 mg./kg. In the next two tests the drug was injected slowly (within two minutes). The doses were 0.25 and 0.5 mg./kg. body weight. Finally, in an attempt to maintain a constant degree of relaxation and to regulate the depth of muscular paralysis at will, a continuous drip of a solution containing 2 mg. per ml. in normal saline was set up. No medication other than oxygen by facemask was given before, during, and after the experiments.

Three members of our medical staff assisted in the tests. One administered oxygen from an anaesthetic machine and conducted the necessary artificial respiration. The second injected the drug and took pulse and blood-pressure readings. The third took eletrocardiographic readings and kept the records. Electrocardiographic tracings were taken before, during, and after the experiments, with the exception of the first two, in which only the blood pressure, pulse, and respiratory rate were recorded.

Results

Experiment 1.—May 11, 1951. 10 mg. S.C.C. (0.125 mg./kg.) injected within two seconds. Effect:—After 30 seconds: onset of muscle weakness, double vision, ptosis, muscle-twitching of eyelids, masseter, arms, legs, and glutei. After 60 seconds: partial paralysis of respiratory muscles; difficulties in speaking; head and arms cannot be raised. After 90 seconds: effect decreasing; good abdominal relaxation. After 120 seconds: arms can be lifted; head still very heavy; respiration still slightly depressed; tone of abdominal muscles returning; speech almost normal; jaw relaxed; eye muscles still weak. After 180 seconds: effect completely worn off. During this experiment no artificial or assisted respiration was necessary. Blood pressure and pulse showed no changes.

*The makers, Oesterreichische Stickstoffwerke A.G., Linz, Austria, kindly furnished the necessary amounts of S.C.C. for these experiments and the clinical evaluation. The drug was named "M115" when in the experimental stage, and has now been registered under the name of "lysthenon."

Experiment 2.—May 11, 1951. 20 mg. S.C.C. (0.25 mg./kg.) injected within two seconds. Effect:—After 30 seconds: generalized fibrillary muscle-twitching in the same sequence as in the first experiment, lasting 5–10 seconds, followed by complete paralysis, including respiration; artificial respiration started. After 60 seconds: first movement of the diaphragm; assisted respiration kept up for approximately another 20 seconds. After 90 seconds: sufficient respiratory exchange with diaphragm only; intercostals and abdominal muscles still paralysed; jaw still completely relaxed; speaking impossible. After 120 seconds: arms can just be lifted; relaxation of abdomen decreasing; speech returning gradually; head cannot be raised. After 150 seconds: still unable to lift head; extremities can be moved freely; jaw still partially relaxed. After 180 seconds: head and eyelids still heavy; speech already distinct and clear. After 240 seconds: no subjective or objective effect left. In this experiment artificial respiration had to be maintained for about 50 seconds. Adequate relaxation for surgery lasted approximately two minutes. The test subject was conscious throughout. There were no side-effects, subjective or objective. Pulse and blood pressure remained almost unchanged.

Experiment 3.—May 12, 1951. 30 mg. S.C.C. (0.375 mg./kg.) injected within two seconds. Effect:—After 30 seconds: fibrillary muscle twitching as in the previous experiments; subjective effect more intensive and somewhat painful; 5 to 10 seconds later complete paralysis of all skeletal muscles; artificial respiration started. After 60 seconds: test subject still completely paralysed. After 90 seconds: diaphragm moving again, but no adequate respiratory exchange yet; assisted respiration for about 20 seconds, then discontinued; jaw and abdominal muscles still completely relaxed; speaking impossible. After 120 seconds: hands and feet can be moved; abdominal wall still soft; head cannot be raised; speech returning gradually. After 150 seconds: as in experiment 2. After 180 seconds: as in experiment 2. After 240 seconds: effect completely worn off. In this experiment artificial or assisted respiration had to be kept up for about 70 seconds. Muscular relaxation adequate for abdominal surgery lasted approximately two minutes. The test subject was conscious throughout. No side-effects, subjective or objective, were noted. The blood pressure remained at the original level throughout. Electrocardiograms showed practically no change in the heart action.

Experiment 4.—May 18, 1951. 20 mg. S.C.C. (0.25 mg./kg.) injected slowly within two minutes. Effect:—After 30 seconds (from start of injection): no effect. After 60 seconds: still no effect. After 90 seconds: eyelids becoming heavy; double vision developing; speaking difficult; extremities can be moved with a little difficulty; head cannot be lifted; jaw relaxed. After 120 seconds: effect less marked; speech clear; some muscle weakness still remaining. After 150 seconds: effect worn off. No muscle-twitching preceded the stage of paralysis this time. The respiratory exchange was adequate throughout, although the intercostal muscles were affected for a short period (20 to 30 seconds). The relaxation of the abdominal wall lasted less than one minute. No changes in pulse rate, blood pressure, and electrocardiogram could be recorded.

Experiment 5.—May 18, 1951. 40 mg. S.C.C. (0.5 mg./kg.) injected slowly within two minutes. Effect:—After 30 seconds (from start of injection): no effect. After 60 seconds: gradual paralysis just starting without preceding muscle-twitching; speech becoming heavy. After 90 seconds: total paralysis has been present for about 10 seconds, artificial respiration started. After 120 seconds: first movement of the diaphragm; ventilation insufficient; assisted respiration continued. After 150 seconds: extremities can be moved; jaw still relaxed; speech returning gradually; head cannot yet be lifted; respiratory exchange adequate with oxygen; assisted respiration discontinued. After 180 seconds: speech normal, distinct, and clear; some muscle weakness still present, particularly in the neck. After 240 seconds (from beginning of injection): no objective or subjective effect apparent. In this experiment also the test subject remained conscious throughout. Although artificial and assisted respiration was necessary for about 50 seconds, pulse, blood pressure, and electrocardiogram remained essentially normal.

Experiment 6.—May 19, 1951. Continuous drip of a 0.2% solution in normal saline, 1 ml. (=20 drops) thus containing 2 mg. S.C.C. When running the drip at a rate of 50 drops a minute (=5 mg. S.C.C., or 0.06 mg./kg. body weight) the onset of muscle weakness was noted about two minutes after the start of the drip. Approximately one minute later diplopia developed, which was followed by marked ptosis and almost complete paralysis of the intercostals. Hands and feet could be moved, but the head could not be lifted. The speech was heavy, but could still be understood. No assisted respiration was necessary. The relaxation of the abdominal wall was comparable to stage III/2 ether anaesthesia. After five minutes the drip was turned off. One minute later the effect was decreasing rapidly, and another minute later it had almost completely worn off.

About 10 minutes later, when there was certainly no residual effect left, the drip was started anew at a rate of 100 drops a minute (=10 mg. S.C.C., or 0.125 mg./kg. body weight). The effect this time began about 90 seconds later with double vision, ptosis, general muscle weakness, and intercostal paralysis, followed about 30 seconds later by total paralysis, including the diaphragm. Artificial respiration was started and the speed of the drip slightly reduced (to approximately 80 drops a minute). An electrocardiogram showed no noticeable changes; the drip was stopped two minutes later. The total muscular paralysis lasted until 30 seconds after the drip had been discontinued. The diaphragmatic movements returned, and recovery in the usual order followed within about two to three minutes. The blood-pressure readings were around 125/80 mm. throughout, as in the previous experiments. The pulse rate slowed down from 74 to 68 a minute.

In these experiments the onset of the effect was slow and gradual, and the initial muscle-twitching was so slight that it was noted only by the test subject himself soon after the drip had been started at the fast rate.

Discussion

The aim of these experiments was to prove the specific action of S.C.C. on the skeletal muscle in man and its freedom from any undesirable side-effects. It could be shown that the muscular paralysis obtained with this drug was regular, quick in onset, and short in duration. In most experiments, particularly when larger dosages were injected rapidly, some fibrillary muscle-twitching, lasting only a few seconds, was observed. This was thought to be the manifestation of the commencing depolarization of the muscle membranes which finally results in greatly diminished response to stimulation of the motor nerves as well as the muscles proper. The mode of action of this compound thus seems to be similar to that of decamethonium.

No side-effects or after-effects were noted. There have been no attributable changes in pulse rate and blood pressure. The electrocardiogram was normal in all tracings. Consciousness was never lost, nor did the drug cause any degree of analgesia, as was proved by pin-prick tests.

Because of the small margin between the relaxing dose and the completely paralysing dose, and because of the rather painful muscle-twitching at the onset of its action, S.C.C. does not appear to be suitable for use in combination with local analgesics. It should be used only by anaesthetists, and the anaesthetic should be administered by means of an anaesthetic machine.

Following these observations in an unanaesthetized man, which proved the usefulness of the new drug as a muscle relaxant, clinical trials on patients under anaesthesia were started.

While this paper was being prepared preliminary reports on 17 cases (Brücke *et al.*, 1951) and 50 cases (Mayrhofer and Hassfurther, 1951) were published. Arnold *et al.* (1951) showed that the drug was also successful in mitigating the convulsions during electric convulsion therapy in psychiatric cases.

We have given up to ten times the paralysing dose to patients under anaesthesia without seeing any side-effects attributable to the drug. Even with these excessive doses the effect did not last longer than 8 to 12 minutes (Mayrhofer and Hassfurther, 1951). We used S.C.C. for all types of operations, and for poor-risk patients as well, and have never encountered any difficulties. Very little thiopentone (up to 0.5 g.) was given for induction, and anaesthesia was maintained with nitrous oxide, pethidine, and, in some instances, an additional trace of ether. No cumulative effect was seen with any of the anaesthetics mentioned.

S.C.C. was particularly useful in facilitating endotracheal intubation, even in difficult patients in whom other curarizing agents had failed to produce adequate relaxation (Mayrhofer and Hassfurther, 1951). Several times it quickly and successfully relieved various degrees of laryngospasm, and in one case it terminated a rather marked bronchospasm following thiopentone induction (Mayrhofer and Hassfurther, 1951).

All patients were awake at the end of the operation; none showed any side-effects or after-effects. The surgeons were extremely pleased with the ideal relaxation for the closure of the abdominal wall; the anaesthetists were particularly satisfied with the complete absence of after-effects and the good respiratory exchange immediately after recovery from paralysis.

Recent reports indicate that a similar short-acting muscle relaxant has been synthesized (Tammelin and Löw, 1951) and tested (Thesleff, 1951) in Sweden. This drug, which has been used for a few months under the name of "L.T.1," is chemically the iodide of succinylcholine. We also used S.S.I. in some of our earlier trials, but since we were afraid of giving our patients too large dosages of iodine we switched to the equally active chloride, which has the additional advantage of being stable in solution.

Summary

Succinylcholine chloride, a new ultra-short-acting muscle relaxant, has been tested in self-experiments. Relaxation is rapid in onset, and the muscles are affected in the same sequence as with other curarizing agents. Its action is similar to that of decamethonium—namely, depolarization of the end-plate region of the skeletal muscles. It is destroyed in the body so rapidly—apparently by enzymatic hydrolysis—that no antidote is needed.

The resulting paralysis lasts from one to several minutes according to the dose. Recovery to full respiratory power occurs within three minutes after the first movement of the diaphragm, even following heavy dosage. Further doses may be given without the risk of dangerous cumulative effects. The drug appears to be free from side-effects or after-effects. Even with doses as high as several times the paralysing dose no changes in circulation could be observed.

The results of our experiments suggest the following wide range of possible uses in clinical anaesthesia.

(1) *To provide relaxation for abdominal and thoracic surgery.*—Time and degree of relaxation wanted are better controlled with S.C.C. than with any other curarizing agent. Its short-lasting effect, however, may be a disadvantage at times when intermittent injection of the drug is not possible. For these cases the use of a continuous drip (0.1 or 0.2% in saline) is recommended.

(2) *To facilitate endotracheal intubation.*—The rapid onset of muscular relaxation and the absence of side-effects render S.C.C. best suitable for this purpose. Yet care must be taken to avoid coughing or "bucking" on the tube owing to the rapid return to muscular power.

(3) *To overcome severe laryngeal spasm.*—Since S.C.C. takes effect within one minute from intravenous injection of the drug, a dose large enough to provide muscular paralysis will certainly cope with any form and degree of laryngeal spasm.

(4) *As an adjuvant in electric convulsion therapy.*—The short-lasting paralysis and the freedom from side-effects make S.C.C. the ideal drug for mitigating the muscle contractions during electric convulsion therapy.

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THE ULTRA-SHORT-ACTING RELAXANTS

BY

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The first English notice about an ultra-short-acting relaxant was a memorandum by Scurr (1951) describing a small trial of di-(β-ethyldimethyl-ammonium-ethyl) succinate diiodide, a close relation of succinylcholine, and, like it and decamethonium, one of the depolarizing group of relaxants (Paton and Zaimis, 1950).

Succinylcholine iodide has been in regular use at the Karolinska Hospital at Stockholm since January, 1951; at the International Congress of Anaesthetists in September, 1951, von Dardel and Thesleff (1951a) reported on 1,000 cases. They are using it to the exclusion of all other relaxants, prolonging its action when necessary by the use of a continuous infusion. One of us (H. R.) saw it in use at Stockholm, and a supply was kindly made available for clinical trial at Cambridge. This report is based on personal use of succinylcholine in 250 cases.

Use in Single Doses

There are now several succinylcholine derivatives in use. It seems probable that doses of all of them containing equal quantities of the active radical have identical effects. The Swedish product, "celocurine," is succinylcholine

iodide; more recently we have also used "scoline," which is the chloride; 100 mg. of the latter is equivalent to 150 mg. of the former.

Our experience confirms the statement of von Dardel and Thesleff (1951b) that "0.5 to 1 mg. of succinylcholine iodide per kg. of body weight induces complete relaxation of all the voluntary muscles for 5 to 10 minutes and necessitates artificial respiration for part of this time." For a patient weighing 12 stone (76.2 kg.) this dose is 37 to 75 mg., and the corresponding dose of succinylcholine chloride is 25 to 50 mg. Smaller doses give briefer as well as less complete relaxation. We believe adequate doses of relaxant drugs always depress respiration to such an extent that it should be assisted or controlled. If this is so, there is seldom any point in giving a minimum dose of such a short-acting relaxant; we usually give a full dose of 100 mg. of succinylcholine iodide to adults. Paralysis is maximal within one minute; its onset is preceded by generalized fibrillary twitchings for a few seconds, such as are observed with the other members of this group. No other side-effects whatever have been observed. Increasing the dose, anyway beyond 150 mg. (100 mg. of the chloride), does not make its effect last any longer, so rapidly is the drug metabolized. It is presumably broken down to succinic acid and choline, both normal metabolites. According to the Swedish report, several thousand times the paralysing dose can be given to animals without any effect on the blood pressure or circulatory system. Recovery is rapid; following an apnoeic dose, the time from the first sign of spontaneous respiration to full normality of all reflexes is not more than three minutes.

It is, however, important to realize that the duration of apnoea following the use of this drug may be prolonged beyond that of its specific effect by the influence of other depressants, especially thiopentone, combined with passive hyperventilation. Indeed, when controlled respiration has been established without using any relaxant it is often possible to maintain apnoea (and abdominal relaxation) indefinitely in a light plane of anaesthesia by hyperventilation alone (Nosworthy, 1941, 1950). The few reported cases of prolonged apnoea following succinylcholine (Love, 1952; Harper, 1952) can perhaps be explained on these lines.

Some Typical Uses for Single Doses

Intubation.—100 mg. of succinylcholine iodide following 0.5 g. of thiopentone usually gives complete paralysis of the vocal cords lasting long enough for an unhurried intubation. Occasionally this dose is found to be insufficient; in this case at least the same amount of the relaxant should be injected again at once, the effect of the initial dose being by now almost at an end. After intubation one must not delay establishing a depth of anaesthesia sufficient to prevent coughing on the tube; the time available can be extended if necessary by giving another dose of the relaxant.

Manipulations and Reduction of Fractures.—For these patients, many of whom are treated without admission to hospital, the combination of full relaxation, light anaesthesia, and rapid recovery is useful. One must, however, never disregard the dangers of profound relaxation, however brief, with a full stomach.

Cephalic Version.—The sequence of thiopentone 0.5 g., succinylcholine iodide 100 mg., and ventilation with oxygen has been used for 12 cephalic versions. When the manipulation was prolonged a second dose of succinylcholine was given. Before this we had been using large doses of gallamine triethiodide as described by Bryce-Smith *et al.* (1951). Succinylcholine gives equally good conditions and more rapid recovery without the need for an antidote.

Electroplexy.—The advantages of an ultra-short-acting relaxant in electric convulsion therapy are obvious. In these cases we aim to adjust the doses of thiopentone and succinylcholine for each patient so that the convulsion is a slight one and is followed almost at once by the return of active breathing. Atropine, 1/200 gr. (0.32 mg.), and hyoscine, 1/200 gr. (0.32 mg.), are injected three-quarters of an hour beforehand. Thiopentone, 0.4 to 0.6 g., is followed after two minutes by succinylcholine iodide, 50 to 100 mg. (or chloride, 30 to 60 mg.). One minute later the shock is applied, a gauze roll having been put between the teeth and the relaxed lower jaw being held up against it. For subsequent treatments the doses are modified as indicated. The lungs are inflated with oxygen during the short period of apnoea. A series of cases are described by Holmberg and Thesleff (1951).

Combination with Other Relaxants.—Succinylcholine used during induction does not interfere with the effect of other relaxants used subsequently. We have also used it, when the effect of an earlier dose of tubocurarine chloride was passing off, to produce a brief return of full relaxation for closure of the abdomen. Under these conditions the pharmacological antagonism between the two relaxants (Paton and Zaimis, 1950) has no detectable influence; when the effect of the succinylcholine has passed, the patient is left in the state one would have expected had it not been used.

Continuous Use

We have maintained relaxation with a continuous infusion of succinylcholine chloride in 0.1% solution for 25 abdominal and six major dental operations. Thiopentone, 0.5 to 0.75 g., is followed by succinylcholine chloride, 75 mg., given with a syringe, the trachea intubated, and the drip started immediately. A rate of about 4 mg. (80 drops) a minute maintains full relaxation. Light anaesthesia is continued by any method suitable for the case in hand. After much greater experience the Swedish workers claim that the rate of infusion can easily be adjusted to give good relaxation without harmful depression of respiration. We still feel, though, that, as with other relaxants, respiration should always be assisted or controlled, and this sometimes makes it difficult to manage the case smoothly single-handed. When the drip stops, reflexes return in full as quickly as after a single dose. This is invaluable at the end of operation, but embarrassing and dangerous if it occurs prematurely. So any accidental failure of the infusion must be corrected within a few minutes or else a longer-acting relaxant must be injected.

In spite of this complication of technique our Stockholm colleagues continue to regard succinylcholine by continuous infusion as superior to all other relaxants. The compensating advantages claimed for it are absence of any secondary effects on the sympathetic, parasympathetic, or central nervous systems or the circulation, absence of histamine-release and immediate recovery of full muscle-tone and reflex activity at the end of operation. There is no other relaxant for which these impressive claims can be made, and our experience convinces us that they warrant further investigation.

Most of the above work was done with "celocurine," kindly provided by the Vitrum Company, of Stockholm. Later Messrs. Allen and Hanburys also provided generous supplies of "scoline," including vials of 500 mg. for mixing with 500 ml. of saline for infusion.

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Guido Banti, the Italian pathologist, was born on June 18, 1852. He made important early investigations on typhoid septicaemia, leukaemia, and pneumococcal infection, but is best remembered for his description of the spleen in splenic anaemia ("Banti's disease," 1882) and of the subsequent hepatic cirrhosis ("Banti's syndrome," 1894). He died in Florence on January 8, 1925.

Medical Memoranda

Use of Hexamethonium Bromide and Decamethonium Iodide with Electroplexy

The following case history is considered to be of interest in that the patient suffered from a psychiatric illness accompanied by severe hypertension, and that the former was successfully treated by means of electric convulsion therapy (E.C.T.) in conjunction with a muscle relaxant, decamethonium iodide (C 10), and a depressor substance, hexamethonium bromide (C 6).

CASE REPORT

The patient, a man aged 56, first noticed in April, 1945, that he was a little deaf in the left ear. Three to four weeks later vertigo developed and Ménière's syndrome was diagnosed. He was subsequently discharged from his job as inspector to an aircraft factory on grounds of medical unfitness and without any disability pension. In the following year he developed tinnitus in the same ear and was given treatment, but without any beneficial effect.

In 1946 he became increasingly nervous, started worrying over trifles, and imagined that all sorts of morbid things were the matter with him—in particular, owing to the noise in the head, that he had a tumour of the brain. In February, 1950, his mother-in-law, of whom he was very fond, died of cancer of the stomach, and for some weeks afterwards he was haunted by the spectre of her painful death. He began to experience difficulty in sleeping, which steadily grew worse. This state of affairs continued for five months until, in August, 1950, he was referred to the psychiatric outpatient clinic, where a diagnosis of involutional melancholia was made; on September 2 he was admitted to hospital.

Physical examination revealed a benign arteriosclerotic hypertension with moderate cardiac hypertrophy; his blood pressure was 260/175. There were no signs of congestive cardiac failure. A moderate degree of kyphoscoliosis and bilateral indirect inguinal herniae were found. No abnormal physical signs were discovered in the C.N.S. The blood urea was 26 mg. per 100 ml., the urea clearance 77%.

During his first four weeks in hospital the blood-pressure recordings were consistently within the range of 240/160 to 260/180, apart from one reading of 180/140, which was taken while he was undergoing a short period of continuous narcosis. During this time his symptoms showed no significant improvement.

It was thought that his insomnia might be predominantly hypertensive in origin, and accordingly on October 11 treatment with oral C 6 was begun. The initial dose was 250 mg. twice a day; this was increased on alternate days until on October 21 he received 3 g. in six divided doses; it was then maintained at this level until discontinued on December 5. During this period frequent blood-pressure recordings fell within the range of 205/135 to 230/150, apart from one recording of 185/130. This latter reading is significant in that his tinnitus on that day was barely perceptible, and throughout the treatment there appeared to be a directly proportional relationship between the blood-pressure reading and the subjective intensity of the tinnitus, the latter being minimal on rising and increasing steadily as the day progressed, but never reaching the pre-treatment level. The only side-effects attributable to the C 6 were considerable drowsiness and some blurring of vision, the former persisting and the latter diminishing when the drug was maintained at the maximal dosage. It was thought that the drowsiness might be due to bromism, and a blood bromide estimation on November 1 gave the level at 75 mg. per 100 ml. During this period there was some diminution of his insomnia, and, whereas previously he had required 2 fl. dr. (8 ml.) of paraldehyde and 6 gr. (0.4 g.) of sodium amytal at night, he was now able to dispense with the former. There was no improvement in the depression.

On November 20, while continuing oral treatment with C 6, E.C.T. was begun in conjunction with 4.5 to 5 mg. of C 10, 0.25 g. of thiopentone, and gr. 1/75 (0.87 mg.) of atropine, given simultaneously four and a half minutes before the shock: his weight was 10 st. 5 lb. (65.8 kg.). The convulsion was so modified that it was evident only in the facial musculature. His systolic blood pressure was 215 before the convulsion, 180 immediately after it, and subsequently rose to 240—that is, higher than the pre-convulsion level but lower than his normal resting level. After two such treatments in one week he felt less depressed and managed to obtain a good night's sleep after as little as 2 gr. (0.13 g.) of sodium amytal. After a third treatment he felt a new man, and a fourth made him mildly euphoric. By this time he was sleeping well after 1 gr. (65 mg.) of sodium amytal. He has received no further treatment since, and C 6 was discontinued after the fourth E.C.T.

DISCUSSION

Although it is too early to assess the permanent result of the treatment the technique was highly successful, and it is this that may be considered of interest. This patient's convulsions were fully suppressed, although he received no more than our standard maximal dose of C 10—that is, 0.5 mg. per stone (6.4 kg.) of body weight—and there would therefore appear to have been no antagonistic action between C 6 and C 10. It is suggested that a single intramuscular injection of C 6 might profitably be given before each shock in cases with severe hypertension if E.C.T. is indicated on psychiatric grounds but contraindicated by the physical condition.

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Purpura and Amyloidosis in Hodgkin's Disease

In Hodgkin's disease the platelet count of the peripheral blood, if altered at all, is usually raised, and cases with low platelet counts and haemorrhagic or purpura diatheses are rare (Hoster *et al.*, 1948). Perlman and Fox (1941) found three cases of Hodgkin's disease among 355 patients with evidence of a haemorrhagic diathesis, and Wright-Smith (1943) described an example of Hodgkin's disease with thrombocytopenia complicating pulmonary tuberculosis. Bodley Scott (1949) referred to the improvement which may result from splenectomy in certain lymphadenopathies with haemorrhagic symptoms. We have had the opportunity of observing a further case of Hodgkin's disease, presenting with thrombocytopenic purpura, improving dramatically after splenectomy, but subsequently dying with extensive amyloid disease.

CASE REPORT

A male clerk aged 28 was admitted to hospital on April 9, 1948, with epistaxis. He had been vaguely unwell for about 18 months with tiredness and breathlessness on exertion, and had lost weight. He had had several attacks of epistaxis—profuse on three occasions. There was nothing relevant in his past or family history.

He was very pale, and there were numerous petechiae of varying ages on his neck, shoulders, chest, back, and arms. The liver was slightly enlarged but the spleen was not palpable. There were some small lymph nodes with a rather elastic feel in the posterior triangle of the right side of his neck, in the right supraclavicular fossa, and in both groins. Clinical examination was otherwise negative; the fundi were normal. His blood pressure was 100/60.

Investigations.—Haemoglobin, 4 g.% (27% Haldane); leucocytes, 8,000 per c.mm. (neutrophils 88%, lymphocytes 10%, eosinophils 1%, monocytes 1%). The morphology of the leucocytes was normal but the red cells were

poorly filled with haemoglobin. Platelets, 51,000 per c.mm. Tourniquet test: positive, bleeding-time (Ivy's method) over 45 minutes; urine—no abnormalities; Paul–Bunnell reaction and W.R. negative; cephalin-cholesterol test negative; serum albumin 3.9 g.%, serum globulin 3.25 g.%; fractional test meal—rather a high acid curve. Radiograph of chest normal; blood group O Rh-positive. Sternal puncture gave the following results: myeloblasts 0.4%, promyelocytes 1%, neutrophil myelocytes 13.2%, neutrophil band cells 26.4%, neutrophil segmented cells 18.2%, eosinophil myelocytes 2.6%, eosinophil band cells 1.8%, eosinophil segmented cells 1.2%, basophil myelocytes 0.2%, basophil segmented cells 0.2%, megakaryocytes 0.4%, lymphocytes 3%, proplasmacytes 1%, plasmacytes 0.2%, reticulum cells 0.8%, cells in mitosis 0.6%, pronormoblasts 1%, basophilic normoblasts 2.8%, polychromatic normoblasts 26%; cellularity increased. A more extended count showed that there were about 4,000 megakaryocytes per million normoblasts, and only 25% of them had evidence of platelet production (granule formation in the cytoplasm being the criterion taken).

PROGRESS AND TREATMENT

Nose-bleeding was severe, and the patient's general condition gave rise to considerable anxiety. After several blood transfusions the epistaxis ceased for a few days, but later recurred, and further transfusions were given. He had irregular temperature up to 101.6° F. (38.7° C.). On May 5 the tip of the spleen was palpable.

By May 13 he had improved slightly, and a laparotomy was carried out by Mr. M. S. Campbell. The patient's nose was not bleeding at the time, but his platelets had dropped to 1,400 per c.mm. The spleen was found to be enlarged, and there were several enlarged para-aortic lymph nodes. The spleen and one of the lymph nodes were removed.

The operation was amazingly effective. Epistaxis did not recur, and the patient's general condition improved rapidly. The platelets rose steadily, and on May 25 had reached 210,000 per c.mm.; the bleeding-time, coagulation time, and tourniquet test gave normal results, and remained normal until his death. On the same day a second sternal puncture showed: promyelocytes 1%, neutrophil myelocytes 19%, neutrophil band cells 37.5%, neutrophil segmented cells 26.5%, eosinophil myelocytes 3%, eosinophil band cells 1%, eosinophil segmented cells 3%, lymphocytes 4%, plasmacytes 1.5%, monocytes 0.5%, polychromatic normoblasts 3%; cellularity normal. There was a big reduction in the proportion of the red-cell precursors. After a careful and prolonged examination only three megakaryocytes could be found, and they all showed evidence of platelet production. On June 1 the absolute eosinophil count in the peripheral blood was 1,300 per c.mm. This was the only time his eosinophils were found to be raised. Apart from a small left-sided pleural effusion which was slow to resolve, convalescence was uneventful, and although his temperature was still not settled, he was discharged from hospital on July 3.

The patient was readmitted on August 9. He was then thin and pale and his skin had an icteric tinge. In addition to the lymph nodes palpated previously there were now some in the left side of the neck and in the axillae. His liver was no longer palpable. Haemoglobin, 10.4 g.% (Haldane 70%); leucocytes, 14,200 per c.mm. (neutrophils 75%, eosinophils 2%, lymphocytes 15%, monocytes 8%); platelets, 380,000 per c.mm.; blood urea, 60 mg. per 100 ml., later rising to 100 mg.

Another lymph node from the neck was removed for biopsy on August 28, and showed tuberculosis. Albumin and hyaline and granular casts were found in the urine on August 31. The serum albumin was then 2.2 g.%, the serum globulin 1.6 g.%; the serum sodium 271 mg. per 100 ml.; and the chlorides (expressed as NaCl) 500 mg. per 100 ml.

Oedema of the legs developed, and loose blood-stained motions were passed. The patient died on September 23.

Pathological Examination of Spleen and Lymph Node Removed at Laparotomy.—Microscopically the lymph node showed a patchily distributed fibrosis and cellular areas which often contained numbers of large multinucleated reticulum cells. The appearances suggested Hodgkin's disease. In places the fibrous tissue showed an advanced degree of hyalinization. Congo red and metachromatic staining for amyloid was negative. The spleen, which weighed 420 g., showed a thickening of the walls of the sinusoids, deposits of haemosiderin, and an infiltration with Hodgkin's tissue similar to that in the lymph node. In some places the Malpighian bodies showed deposits of hyaline tissue. Stains for amyloid were again negative.

Post-mortem Findings.—In the thorax there was only one enlarged paratracheal lymph node, but in the abdomen there was a large mass of them in the hilum of the liver, along the upper border of the pancreas, and beside the aorta. There were some old pleural adhesions, and the pericardial sac was obliterated by organizing adhesions. There was a bicuspid aortic valve with a recent acute bacterial vegetation. Some atheroma of the coronary arteries was present. The liver (weight 2,436 g.) was congested and firm, and histologically showed typical amyloid changes. The kidneys each weighed 425 g., and also showed amyloid changes. The marrow was hyperplastic, but contained no deposits of Hodgkin tissue. Lymph nodes showed Hodgkin's disease and a caseous one tuberculosis. The other organs examined showed no special features.

COMMENT

Before splenectomy the marrow showed a great increase in the number of megakaryocytes over the normal figures as given by Dameshek and Miller (1946), and the percentage showing evidence of platelet production was greatly reduced. After splenectomy the marrow picture reverted to a more normal type, apart from the reduction in the red-cell precursors. The progress of this case agrees with the views expressed by Bodley Scott. Haemolytic anaemias associated with Hodgkin's disease also frequently do well after splenectomy, but one of the cases referred to by Bodley Scott subsequently died with amyloid disease.

The development of amyloid in association with Hodgkin's disease has been noted by several authors from time to time. In recent years cases have been mentioned by Lehman (1943), Cervera and Podestá (1946), and Jackson and Parker (1947). In our case it developed late in the course of the disease and was associated with tuberculosis. This association with a chronic bacterial infection is not evident in all cases, but it would seem probable that, if a large part of the reticulo-endothelial system is disorganized by a reticulosis, abnormal proteins in the plasma, produced perhaps in the presence of quite a minor infective focus, would not be dealt with efficiently, and amyloid storage would occur.

Our thanks are due to the Director-General of Medical Services, Ministry of Pensions, for permission to publish this case; to the several clinicians who examined this patient and made their notes available to us; and especially to Professor M. J. Stewart for much helpful advice and for permission to quote some of the findings from his department.

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Reviews

SEXUAL BEHAVIOUR

Patterns of Sexual Behavior. By Clellan S. Ford, Ph.D., and Frank A. Beach, Ph.D. With an introduction by F. A. E. Crew, M.D., D.Sc., Ph.D., F.R.S. (Pp. 307. £1 2s. 6d.) London: Eyre and Spottiswoode. 1952.

Kinsey and his collaborators gave us a detailed statistical survey of sexual behaviour in the human male so far as one important Western culture—North America—was concerned. The authors of *Patterns of Sexual Behavior* have attempted to cover the whole field by providing an objective account of sexual activities based on the study of 190 societies and a great number of mammalian species. Clellan S. Ford is assistant professor of anthropology in Yale University, and his co-author, Frank A. Beach, is professor of psychology in the same university. Professor F. A. E. Crew, of Edinburgh, provides a short foreword.

The book, which makes no pretensions to being encyclopaedic, is strictly factual and sedulously eschews moral evaluations. Moreover, theoretical interpretations of a psycho-analytical or of any other nature are carefully avoided.

This valuable and courageous study should prove to be a classic of its kind for many years to come. Information concerning the evolution, the physiology, and the sociology of the sexual functions which was hitherto scattered here and there and hard to come by is now for the first time collected together between two covers and arranged in such a way as to unfold a meaningful pattern which has relevance not only for literate societies but for pre-literate communities, the primates, and certain other mammals as well.

Without reference to the *moral* rightness or wrongness of any particular sexual pattern, this book teaches us to be extremely wary of employing terms such as "unnatural" or "perversion" with any scientific meaning. For instance, with regard to sexual self-stimulation, we learn that some kind of masturbation occurs in all the human societies mentioned in the book and in many infrahuman primates and other mammals. In some human societies masturbation in childhood is condoned or even encouraged, whereas in others it is strongly condemned. In nearly all cultures masturbation in adult life comes in for some disapproval, which ranges from mild ridicule to severe sanctions. Masturbation, for a variety of reasons which are analysed by the authors, would seem to be more common in the male than in the female.

Again, we find that homosexual behaviour occurs in nearly all human societies and in apes and monkeys, both in the free state and in captivity. Some human societies, such as our own, condemn all manifestations of homosexuality in both sexes and at all stages of life; others condone it in childhood and condemn it in adulthood; yet others actively impose homosexual practices on all its male members. As it is the duty of a conscientious reviewer to point out small mistakes in a book, if he can spot them, if only to show how carefully he has read it, it should be pointed out that the word paederasty means homosexually coloured love of boys and not "homosexual anal intercourse," as it is defined in the glossary. Paedicatio is the correct term for anal coitus.

It would seem that in view of the complicated structure of the cortex in man and the higher primates, learning, as opposed to simple instincts, plays a more important part in behaviour than was previously recognized. On this point the authors say: "Far the most of what people learn to feel and to do in the realms of sex is learned from other individuals. Human learning, in other words, customarily occurs in a social context. For this reason the impact of learning upon human sexuality is best understood within the frame of reference provided by the societies of which the individual is a member."

E. B. STRAUSS.

PREVENTIVE MEDICINE

Rosenau's Preventive Medicine and Hygiene. 7th edition. By Kenneth F. Maxcy, M.D., Dr.P.H. (Johns Hopkins), and 26 Collaborators. (Pp. 1,462; 131 illustrations. $14.) New York: Appleton-Century-Crofts. 1951.

The late Dr. Milton J. Rosenau produced the first edition of his book on preventive medicine in 1913. This and subsequent editions were so acceptable to public health workers in the United States, the British Isles, and elsewhere that the book became widely recognized as the most authoritative publication on preventive medicine in the English language. But Dr. Rosenau's last edition was published 16 years ago, and much has happened since then. Dr. Maxcy, professor of epidemiology at the Johns Hopkins University, accepted the heavy responsibility of this new edition, and he has succeeded so well that "Rosenau" has regained its former supremacy. Dr. Maxcy has been assisted by a team of distinguished collaborators, masters of their respective subjects, providing together an unparalleled wealth of ability and experience in preventive medicine.

The first section is a well-written and comprehensive treatise on the prevention of communicable disease. It will be valued by the British reader for the description of the rarer diseases as well as of the more common infections. There is, to take but a sample of this section, an excellent and concise account of the history and present position of the prophylaxis of whooping-cough, including the pioneer work of Dr. Pearl Kendrick and research in England conducted in recent years by the Medical Research Council. The potential value of a mouse protection test for assessing the potency of pertussis vaccines is discussed. Unfortunately, the mouse test has not so far provided a reliable index of the level of protection given to vaccinated persons. If this should prove to be possible, it would be a long step towards the perfection of whooping-cough immunization.

The maternal and child health services are soundly reviewed, but their importance is surely such that they need and deserve a much greater share than they get of the many pages of this large book. The chapter on atmospheric pollution is both salutary and instructive, and will appeal strongly to those interested in smoke abatement in Britain.

If space permitted, it would be both just and pleasurable to comment appreciatively and at length about the many other excellent features of this book. Suffice it to say that it is an admirable and remarkable production—a combined textbook and work of reference which will be welcomed by all interested in preventive medicine. The publishers are to be congratulated on the superb quality of the paper, printing, and binding. They have made a volume which will adorn any bookshelf and provide the book lover with a new book to cherish.

C. METCALFE BROWN.

A MAN OF WRATH

Dr. Viper. The Querulous Life of Philip Thicknesse. By Philip Gosse. (Pp. 332; 7 pages of half-tone illustrations. £1 1s.) London: Cassell and Co. 1952.

It may be a disappointment to medical readers to discover that Dr. Viper was neither physician nor apothecary. Philip Thicknesse, known to a cloud of adversaries as Dr. Viper, was, however, in boyhood an apothecary's apprentice and in later life maintained a lively and unorthodox interest in disease. He cured the great Lord Thurlow of gall-stones by a regimen of horse-trotting ("which rendered the externals of the gall-stones perfectly smooth") and by the free use of laudanum. Samuel Foote, the actor and playwright, lampooned him by the name of Dr. Viper in his play *The Capuchin* and also wrote of him that "he had the stupidity of an owl, the vulgarity of a blackguard, the obdurate heart of an assassin, and the cowardice of a dunghill cock."

Dr. Philip Gosse loves the English eccentric, and in Thicknesse he has collected a particularly fine example. Soldier, traveller, and journalist, he ranged widely through the eighteenth-century scene, cherishing affronts, provoking insults, and making enemies of his friends. A critical versifier wrote of him:

> They say I'm a quarrelsome Fellow,
> God rot it, why how can that be ?
> For, I never quarrel with any
> But all the world quarrels with me.

The ripples of daily existence were by his passionate behaviour whipped to a tempest, and when he encountered a man of like temperament to himself, as he did in James Makittrick Adair, a Scots physician practising in Bath, the battle was violent and lifelong. They dedicated books to each other and their dedications were as bludgeons. Adair was a "base defamer, vindictive libeller, a scurrilous, indecent, and vulgar scribbler" with "a lewd and wanton daughter"; Thicknesse, "a celebrated Gout Doctor, Rape and Murder Monger" who "scatters his dung with an air of Majesty."

Now and again, this ardent controversialist was disappointed in his adversary, and how effective are the soft answer and the other cheek in such quarrels can be seen in his encounters with Thomas Gainsborough, with Dr. Moore the Archbishop of Canterbury, with Lord Bateman, and with the Prince de Ligne. Our biographer admits that his hero was an opium addict, a blackmailer, and a crook who cheated his own son. He might have forgiven his son the inheritance through his mother of a peerage and £2,000 a year, but he could never forgive him for being the victim of a father's swindle, and on the title-page of his book, *Memories and Anecdotes*, he describes himself as "late Lieutenant Governor of Land Guard Fort and unfortunately Father to George Touchet, Baron Audley."

Unshaken by such iniquities, Gosse describes him also as a man of character and intelligence, as a husband who lived devotedly with three successive wives, as a kindly and observant traveller, as a humane commander who allowed no flogging of his soldiers, and as the discoverer of the genius of Thomas Gainsborough. Philip Gosse is not a moralist who condemns or a psychologist concerned with the springs of human behaviour, but he is a fine naturalist who portrays the human character as skilfully as his grandfather painted his sea-anemones. This is a book to buy if your guineas are ample, and, if not, one for the top of the library list.

D. V. HUBBLE.

ANTIBIOTIC THERAPY

Antibiotic Therapy. By Henry Welch, Ph.D., and Charles N. Lewis, M.D., with a foreword by Chester F. Keefer, M.D. (Pp. 562; illustrated. $10.) Washington: The Arundel Press. 1951.

In the earlier chapters of this book the authors describe the principal antibiotics in the order of their discovery, each chapter being prefaced by a biographical note and a portrait of the discoverer. The only other illustrations are diagrams representing absorption, circulation, and excretion, and purporting to represent the sensitivity of different genera or species to each drug. These diagrams are unhelpful, since they show only ranges over which sensitivity varies, the extremes being obviously abnormally high sensitivity and a high degree of acquired resistance. Thus the inhibitory concentration of chloramphenicol for "*Escherichia*" is given as 0.2—250 μg./ml. (and for *Clostridia* as 0.1–500 !), whereas it would have been more useful to say that most strains of *E.* (*Bact.*) *coli* are inhibited by about 5 μg./ml.

Few of these findings are referred to in the text, and the true susceptibility of various micro-organisms to each drug can therefore only be inferred from the clinical chapters which follow. In these the authors discuss individual diseases or groups of infections, and include descriptions of clinical features, methods of diagnosis, and general treatment which seem out of place. Thus the chapter on tuberculosis begins: "Tuberculosis is an infectious disease caused by the tubercle bacillus," and continues for six pages before chemotherapy is mentioned. There are well-documented accounts of the results obtained with each antibiotic, but when several are applicable the authors rarely commit themselves to a preference for any one of them. Dosage is carefully specified for each condition. Much space could have been saved by describing systems of dosage in a separate section and referring to them thereafter by symbols, but perhaps this would have been inconsistent with the mixed metaphorical promise on the dust cover: "Allowances for the individual patient are tailored for the reader in a direct signposted path from the disease to the prescription."

It may seem ungracious so to criticize a book which is for the moment the best source of information on its subject, but it could be so greatly improved by deletions and condensation of some parts, and by expansion of those which deal with the choice of an antibiotic for a particular purpose. Its most useful features are a profusion of clinical information about the newer antibiotics, accounts of results obtained in many uncommon diseases, and descriptions of several antibiotics almost unknown outside the United States.

L. P. GARROD.

THYROTOXICOSIS

Thyreotoxikosen und Antithyreoidale Substanzen. By Professor Hans Wilhelm Bansi. (Pp. 100. M. 11.40.) Stuttgart: Georg Thieme. 1951.

It seems strange to be reviewing a book from the pen of a professor of medicine at Hamburg, the cleavage having been so complete for so many years. The subject being thyrotoxicosis and antithyroid substances, it is appropriate that the first sentence acknowledges the pioneer work of our Boston colleague, Astwood, and the bibliography shows a good knowledge of Anglo-American literature. There is nothing especially new for English readers. The recommended control tests of repeated blood counts, basal metabolism, and cholesterol have not been assiduously practised outside hospitals, and the first rarely permits anticipation of agranulocytosis, which comes like a bolt from the blue. It is of interest that American workers have found that agranulocytosis may respond to A.C.T.H. The author discusses on clinical lines the evaluation and limitations of thiouracil therapy and the indications for surgery. The book will serve a useful purpose and constitutes a reliable and not unduly verbose treatise on the subject.

S. LEONARD SIMPSON.

PLASTIC SURGERY FOR NURSES

Plastic Surgery: An Introduction for Nurses. By C. R. McLaughlin, M.B., Ch.B., B.Chir., F.R.C.S.Ed., with special sections by other members of the Queen Victoria Hospital Staff and illustrations by R. H. Dale, M.A., M.B., B.Chir., F.R.C.S.Ed. (Pp. 125; 32 figures. 12s. 6d.) London: Faber and Faber. 1951.

The author describes in simple terms the problems which will confront all nurses in a hospital specializing in plastic surgery. It is interesting that there is an apparent return to the classification of burns into three degrees in a hospital which was so outstanding in the treatment of this condition during the war. The general methods of treating facial fractures and the technique of most of the simple operations of plastic surgery are well described, and this is done in such a way as to make it possible for the nurse to have a clear idea of the problems with which she will be faced in the post-operative phase. There is a special section on theatre methods and on anaesthesia. Any nurse thoroughly familiar with the contents of this book would have little difficulty in the practical application of her knowledge.

RAINSFORD MOWLEM.

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OUR PATRON THE QUEEN

The Keeper of the Privy Purse at Buckingham Palace has informed the Secretary of the British Medical Association that the Queen "has been graciously pleased to grant her patronage to the British Medical Association." The first Royal Patron of the Association was King Edward VII, and so Elizabeth II is the first queen to honour the Association in this way. She has already shown her special interest in medicine by accepting the Honorary Fellowship of the Royal College of Surgeons and of the Royal College of Obstetricians and Gynaecologists. All members of the B.M.A. will hope that the years of the Queen's patronage will be long and that during them the bonds which unite the medical profession within the Commonwealth will grow stronger than ever.

THE SECRETION OF MILK

The study of lactation is a field in which human physiology and agricultural physiology have common ground. Recent interesting advances in dairy science may help in clinical practice, or at least throw light on human pathology. Some years ago it was found[1] that udder growth and lactation could be caused in farm animals merely by treatment with synthetic oestrogens. Though occasional spectacular successes were obtained on an experimental scale, these were not regular enough to warrant optimism about the use of this treatment for getting commercial milk yields from sterile animals. Recent progress in the cheap large-scale production of progesterone from plant sources has, however, made it possible to see if better results can be obtained from the combined use of oestrogen and progesterone. Work on goats[2] indicates that, while udders exposed to oestrogen alone are abnormal histologically and probably deficient in the total area of secretory epithelium, combination with progesterone reduces considerably the incidence of histological abnormalities and produces mammary tissue with smaller alveoli and hence a greater alveolar surface per unit volume. A regimen of treatment with both hormones may therefore soon be evolved which will be much more certain in inducing udder growth and lactation. Already, in the United States two sterile cows artificially brought into lactation by such means have given peak daily milk yields of 8 and 4½ gallons respectively.[3] The possibility that these discoveries may have applications in human medicine must not be ignored.

When the anterior-pituitary lactogenic hormone, prolactin, was purified it was hoped that it would be of value in the treatment of hypogalactia in women. These expectations, based on a belief that prolactin would possess galactopoietic activity, have, however, not been realized, and prolactin to-day is very little used by clinicians. This is now understandable in the light of recent experiments on lactating cows, which suggest that prolactin *per se* has in fact little, if any, galactopoietic activity.[4] On the other hand, unfractionated ox anterior-pituitary extracts cause considerable stimulation of lactation, and it now transpires[4] that much if not all of this activity must be ascribed to the growth hormone present in these preparations. Thus, somatotrophin, besides stimulating growth or perhaps inducing diabetes according to circumstances, also exhibits galactopoietic activity, a finding which confirms the previous prediction of Young[5] that all three processes, requiring as they do a similar type of metabolic control involving a restraint on the oxidation of foodstuffs, may be related to a common pattern of hormonal regulation. Clinical trials of somatotrophin in the treatment of hypogalactia might well be worth while, provided the possibility of also producing diabetes is not overlooked.

Another phase of lactation, until recently ill-understood, but the importance of which is becoming increasingly apparent, is illustrated by Tintoretto's famous picture, "The Origin of the Milky Way." It shows a woman with a child suckling one breast while from the other gushes a stream of milk; thus has a great artist depicted the milk-ejection reflex. This reflex is of equal importance to clinician and farmer, since upon its efficient functioning depends the success of lactation. Once believed to be a purely neural affair, it is now known to be a neuro-endocrine

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reflex, involving activation of the neurohypophysis by afferent impulses from the teat. That neurohypophysial activation takes place is evident from the facts that milk ejection can be evoked by injection of posterior-pituitary extract[6] and that antidiuretic effects have been seen in women[7] and cows[8] soon after application of the suckling stimulus. Which of the known neurohypophysial hormones is concerned is uncertain, though the bulk of the evidence points to oxytocin. The neural pathways involved in this stimulation of the posterior lobe have been studied by Cross and Harris[9] in Cambridge and Andersson[10] in Stockholm, who have shown that milk ejection may be evoked by electrical stimulation of the pituitary stalk or hypothalamic centres adjacent to the supraoptic nuclei, while electrolytic lesions placed suitably in the supraoptic-hypophysial tract abolish the reflex though milk ejection can still be evoked by injection of posterior-pituitary extract. There is also the histological work of Richardson,[11] which has made it virtually certain that the effector contractile tissue of the mammary gland consists of myoepithelial cells ("basket cells") forming a network over the outer surface of the alveoli, and responsive to oxytocin.

There have also been interesting developments in the biochemistry of milk secretion in recent years. While it is true that the mode of formation of milk protein is still obscure there are signs that the enigma of lactose formation will soon be solved. For the precursor of lactose there seems to be no need to look beyond glucose entering the gland from the blood or fabricated *in situ* from small molecules; the chief problem is the origin of the galactose half of the lactose molecule, which differs from the glucose half only in the spatial arrangement of the atoms attached to its fourth carbon atom. The brilliant studies of Leloir and his associates[12] in Buenos Aires have revealed the existence in yeasts and muscle of an enzyme, "galactowaldenase," which might well be capable of causing the transformation of glucose into galactose, while ingenious use by Stetten[13] of galactose labelled with C^{14} has done much to indicate that the transformation does not involve the fragmentation of the glucose molecule.

It is, however, in our knowledge of the biosynthesis of milk fat that the greatest advances, amounting almost to a revolution, have occurred. Milk fat was once believed to originate solely from the glycerides of the blood. Since the fatty acid "spectrum" of milk fat differs from that of body fat in that it contains fatty acids with shorter carbon chains than any known to occur elsewhere in the body, the theory of the origin of milk fat from blood fat carries the corollary that the latter must undergo chemical transformation in the mammary gland. Thus the characteristic volatile fatty acids of milk fat were believed to be formed by degradation of long-chain blood fatty acids in the udder.[14] Recently, however, various lines of evidence have been brought forward which show that the mammary gland synthesizes fatty acids from small molecules and that this process is of prime importance in the biosynthesis of milk fat. Respiratory measurements[15] and tracer studies[16] alike prove that acetate and carbohydrate are important precursors of milk fatty acids, the mammary tissue effecting the chain elongation by successive addition of 2-carbon units.[17] Thus blood fat is not the source of the volatile short-chain fatty acids of milk, which rather represent intermediate stages in the synthesis of long-chain fatty acids. It is surely significant in this connexion that short-chain fatty acids are found in greatest amounts in the milk fat of ruminants, which are known to absorb large quantities of acetate produced by the breakdown of plant polysaccharides by bacteria in the rumen.

"NEGLIGENCE" IN HOSPITAL

In a recent letter to *The Times*[1] Professor Ian Aird discussed the unfortunate effects of the word "negligence" upon the relations between hospital governing bodies and their consultant staffs who find themselves involved in actions by patients who are dissatisfied with the results of treatment which they have received. He suggested that a formula should be found to replace the word "negligence," in order to facilitate agreement between boards of governors or hospital management committees and their medical staffs and so reduce such actions into "a plain issue between plaintiff and defendants rather than the common free-for-all contest between defendants striving to avoid the stigma of negligence which is now so commonly seen."

Commenting on Professor Aird's letter, the secretary of the Medical Protection Society pointed out that negligence means in law a breach of the duty to take reasonable care, having regard to the accepted canons of professional skill obtaining at the time, which all professional men owe to others in their work.[2] He quoted a recent judgment in which the Lord Chief Justice had stressed that charges of negligence against professional men were very serious allegations, and ought not to be made unless there was a clear case of failure to exercise the skill which

[1] *The Times*, May 23, 1952.
[2] Ibid, June 3.
[3] 1951 2 K.B. 343.
[4] *British Medical Journal*, 1951, 1, 480.
[5] 1909 2 K.B. 280.
[6] 1942 2 K.B. 193.

an ordinary practitioner of the defendant's standing and position would exercise. It did not follow that because an accident happened the operator was negligent, and "no practitioner is an insurer that no accident would happen." If, however, the injury was brought about by a disregard of ordinary professional skill and competence, then the plaintiff was entitled to recover damages against the practitioner.

The law, then, is clear on what is negligence, but, as Professor Aird observes, the word has an ugly flavour to a professional man. The reason for this is not necessarily because the public at large understands by the word some degree of criminal culpability, even if that be so, but because he is being accused of falling short of his proper professional standards. The main reason which Professor Aird puts forward for seeking an alternative formula in place of "negligence" is that it would reduce the difficulties which arise when the plaintiff makes his claim not only against the hospital governing body but also against a member of its consultant staff; or when the governing body, faced with a claim, in its turn inculpates a member of its consultant staff. The necessity for making the member of the consultant staff a party to the action arises, writes Professor Aird, from the fact that the hospital governing body is not responsible in law for the professional actions of its consultant staff. But is this correct? The decision of the Court of Appeal in Cassidy *v.* Ministry of Health[3,4] was an important one, and when the point is next considered the law will probably be that a hospital governing body or management committee is just as much responsible for the acts of its consultant staff as it is for the acts of its whole-time professional medical and nursing staff. In his judgment Lord Justice Denning explained the responsibility of the hospital authority by showing that it cannot carry out its duty to take reasonable care of the patient except by the staff it employs. It has no ears of its own to listen through the stethoscope, and no hands of its own to wield the surgeon's knife. It is no answer for the authority to say that its staff are professional men and women who tolerate no interference by their lay employers in the way they do their work. All this, said Lord Justice Denning, seemed so clear in principle that he wondered why there should ever have been any doubt about it. Yet from 1909 until 1942 it had been the general opinion of the profession, based on the judgment of Lord Justice Kennedy in Hillyer *v.* St. Bartholomew's Hospital,[5] that hospital authorities were not liable for negligence of their staff in the course of their professional duties. In 1942 a distinction was drawn between whole-time and consultant professional staff in Gold *v.* Essex County Council.[6] The judgment of Lord Justice Denning in Cassidy's case shows that in principle there is no such distinction. In future, therefore, it would appear that any prospective plaintiff who is aggrieved by his treatment in hospital need bring his action only against the hospital authority, which will be equally responsible whether it turns out that his injury was caused by the negligence of a nurse, a house-surgeon, or a consultant.

BRIEF FLACCIDITY

British anaesthetists have now had time to evaluate the ultra-short-acting relaxant drugs which were introduced from the Karolinska Institute, Stockholm, last year.[1] These agents are salts of succinylcholine, and act by depolarization of the muscle membrane in the same way as the methonium group of relaxants. The effect of a single dose lasts for only two or three minutes, and flaccidity is preceded by brief generalized muscular twitching. There appear to be no side-effects on the peripheral and central nervous systems, nor on the circulation. Elsewhere in this issue Dr. O. K. Mayrhofer describes the self-administration of succinylcholine chloride ("scoline"), and Drs. H. Richards and H. R. Youngman report the use of succinylcholine iodide ("celocurine") and succinylcholine chloride in 250 cases. Richards and Youngman found that a single dose of either drug gave satisfactory relaxation for endotracheal intubation, orthopaedic manipulations, the reduction of fractures, cephalic version, and electroconvulsion therapy, and for closure of the abdomen when the effect of D-tubocurarine chloride had passed off. They also used a continuous infusion of succinylcholine chloride as 0.1% solution in normal saline as the sole relaxing agent for abdominal operations—a technique which affords the anaesthetist closer control than with the longer-acting relaxants, and ensures that the patient's reflexes and muscle tone return at the end of the operation without the injection of neostigmine. There is no antidote to the succinylcholine compounds, and it is sometimes necessary to continue inflation of the lungs after their use for much longer than would be expected; three such cases have been reported, in which the patients were given between 60 and 100 mg. of succinylcholine chloride.[2-4] In the correspondence pages this week Drs. F. F. Foldes and J. Kennedy Harper argue whether the cause of this apnoea is overdosage or imperfect hydrolysis of the drug, and Richards and Youngman suggest it may be due to the depressant effect of thiopentone and to hyperventilation. But a true variability in the action of the succinylcholine compounds seems to exist, and anaesthetists might be wise to administer a test dose. Certainly to give such drugs with thiopentone or another anaesthetic for short and minor procedures (such as the reduction of a dislocation) for the sake of the brief effect without having the means of inflation at hand is to court danger.

[1] *British Medical Journal*, 1951, **2**, 668.
[2] Ibid., 1952, **1**, 866.
[3] Ibid., 1952, **1**, 971.
[4] *Anaesthesia*, 1952, **7**, 113.

BACTERIA AT THE SEA BOTTOM

Pathogenic bacteria are but a small fraction of all the bacteria on the earth. The great multitude of harmless species has, however, received scant study, although the bacteria of soil play an important part in the fertility of the land, and many produce curious chemical changes so that they can live almost anywhere. Who, for example, would have imagined that a living cell would make use of hydrogen sulphide in place of oxygen, converting it to free sulphur or sulphate in the course of photo-synthesis, as the purple bacteria do?

The latest report[1] is of bacteria from the sea bottom. A cover and grab have been lowered from a ship to the bottom of the Philippine Trench, a deep cleft 100 miles long and two miles wide in the floor of the Pacific Ocean, and samples of mud brought up for culture in sea water enriched with peptone, beef, and yeast extract. So far down—over 10,000 metres (34,000 feet)—there is no light, the temperature is always about 2.5° C. and the water pressure about 1,000 times atmospheric pressure. The cultures were therefore incubated at this high pressure and cool temperature as well as at 30° C. and one atmosphere, and anything from 10 to 100 times more bacteria grew under the conditions of great compression. Species of *Pseudomonas, Clostridium, Spirillum, Vibrio,* and *Micrococcus* were among those identified.

This is not the first time by any means that bacteria have been cultivated from such depths, though the Philippine Trench holds the deepest water record. Nor are they the only living organisms on the bottom, since certain crustaceans, worms, and echinoderms have also been recovered, but unfortunately were dead by the time they reached the surface. It has been suggested that the deep-water bacteria serve as an important food for these animals.

[1] ZoBell, C. E., *Science*, 1952, **115**, 507

"THE EASY APPROACH"

One of the pleasant features of the life of medical societies is the annual gathering round the dinner-table, when old friends may meet and at the same time have the opportunity of listening to the after-dinner speeches of the eminent. The spirit of good fellowship usually prompts the speakers to reflections that are gay rather than grave. But at two recent dinners Lord Radcliffe and Lord Woolton took the opportunity to show their concern about the present trends in medicine and in the changing fortunes of the professional world. Last week at the annual dinner of the Hunterian Society Lord Woolton said that when he was Minister of Reconstruction he had much to do with the framing of the National Health Service Acts, although, of course, he was not responsible for the final appearance of these under the Ministry of Mr. Aneurin Bevan. Lord Woolton was sure that it was sound to remove the financial bar that might be in the way of anyone requiring medical treatment. He welcomed this "easy approach" to medical care, but showed his apprehension lest this, along with other benefits of the Welfare State, might weaken the moral strength of the country. More and more were people turning to the State for those things which they previously had to provide for themselves through their own efforts. With the exception of the clergy, Lord Woolton said, the medical profession had a greater influence than anyone else over the people in this country, and it rested more and more upon the individual doctor, through his work, to strengthen the moral fibre of the nation. In his remarks Lord Woolton showed that he shared the concern of many other thoughtful people about the moral climate of the Welfare State, and he put the point neatly when he said that when people used to pay their doctors they treated them with more respect than they appear to to-day. This is the acute problem of our British society. Humanitarian motives have guided the three main political parties to accepting the ideals which lie behind the Welfare State, but this conception seems to embrace principally or entirely material benefits. But the less the individual has to rely upon his own efforts and the more he is encouraged to lean back for support on the paternal state, by so much the more will his sense of personal responsibility be diminished and by so much the less will he tend to rely upon his own efforts. The more he (apparently) gets for nothing the more he will expect to receive for nothing, and it may well be argued, as so many have suggested, that the sick person should make some direct payment, however small, for the care he receives when he is ill. Lord Woolton was right in sounding a note of warning about the weakening of moral fibre that may come from an excessive relief of personal responsibility.

Is our own profession free from the same contamination? The more the State takes over the financial responsibility of the medical profession the more, too, shall we run the risk of a lessening of responsibility and a whittling away of those ideals of a great profession which have grown up over the centuries. As Lord Woolton put it, the professional man has his rightful desire for independence and takes pride in securing for himself something of the judgment of excellence bestowed upon him by his fellow men. It was the time-honoured part of the family doctor to be someone who was sought after and not someone who was commanded. Lord Radcliffe, when he spoke at the Medical Society of London in March, made the depressing observation that the learned professions were "a dying industry." He saw the ideals of a factory civilization creeping in and the danger that people might come to forget and neglect the traditions and codes built up over the years by the learned professions.

TRIETHYLENE MELAMINE

Nitrogen mustard (methyl-di-2-chloroethylamine) is now in general use as a palliative agent in generalized Hodgkin's disease, lymphosarcoma, and to a lesser extent in the chronic leukaemias and polycythaemia vera. Individual remissions, especially in Hodgkin's disease, may last for six months to one year. Repeated courses of the drug may be given, though later responses tend to be progressively less satisfactory. With careful management some patients for whom the outlook seems hopeless may be kept in fairly good health for as long as two years after other methods of treatment, especially

radiotherapy, have lost their efficacy.[1] Treatment with nitrogen mustard has several disadvantages: first, it must be given intravenously, and even with scrupulous care the veins eventually become thrombosed; secondly, it often causes nausea and vomiting which may be extremely distressing in debilitated patients; thirdly, some degree of bone-marrow damage is unavoidable, and, although usually transient, it may be severe enough to preclude further treatment.

Attempts have been made, with disappointing results, to alter the chemical structure of nitrogen mustard so as to preserve or enhance its therapeutic effects while abolishing both the toxic action on bone marrow and the incidental side-effects on veins and gastro-intestinal tract. The first promising compound active when taken by mouth was the β-naphthylamine analogue of nitrogen mustard known as R.48. This was one of many aromatic analogues synthesized and studied experimentally in tumour-bearing animals by Haddow and his colleagues[2] at the Royal Cancer Hospital in London. Nausea and vomiting are rarely caused by R.48, but its relatively feeble therapeutic action does not compensate for its low toxicity. A more effective substance is 2:4:6-tri-ethyleneimino-1:3:5-triazine, known as triethylene melamine (T.E.M.) in the United States and as M.9500 or R.246 in this country. This substance was used in Germany during the last war as a cross-linking agent in the textile industry to improve the physical properties of fibres. Since the war its biological properties have been studied independently on both sides of the Atlantic. In America its activity, like that of nitrogen mustard, to which triethylene melamine is closely similar, was thought to depend on the presence of the ethyleneimonium ion in solution.[3] In England, Ross[4] had already cast doubt on this view as a result of his work on the aromatic nitrogen mustards, which retain the biological activity of the aliphatic compounds yet do not ionize in solution to any significant extent. His interest in triethylene melamine was stimulated by its cross-linking property, which it was thought might throw light on the mechanism underlying the biological effects of the nitrogen mustard series.[5]

The results of several clinical trials have now been published.[6-10] All investigators agree that triethylene melamine has similar therapeutic activity to nitrogen mustard in Hodgkin's disease and lymphosarcoma and is probably superior in the treatment of chronic leukaemias. Weight for weight it is considerably more potent than nitrogen mustard, but intravenous injections do not cause nausea or vomiting, provided that not more than 2 mg. is given at a time: five injections spread over one month constitute an average course. Unlike nitrogen mustard, triethylene melamine does not damage the veins even after repeated injections. Furthermore, it is active when given orally: 2.5 to 5 mg. is taken one hour before breakfast, and the dose is repeated at intervals of 1–7 days until a total of 20–30 mg. has been given. Gastro-intestinal disturbance is much less troublesome than after the administration of nitrogen mustard. These features are sufficient to establish the practical advantage of the drug over nitrogen mustard, which it may eventually replace, although its therapeutic superiority is not so great as was once hoped. Unfortunately triethylene melamine is an exceedingly powerful bone-marrow depressant, and even doses well within the therapeutic range may cause a profound hypoplasia affecting all elements which often persists for several months if the patient survives the hazard of agranulocytosis. Thus the activity of the substance when given orally—its greatest advantage over nitrogen mustard—is also its greatest drawback, for, as Paterson and Boland point out,[6] "it might be used without the constant supervision and check of blood counts which is necessary."

[1] Nabarro, J. D. N., *Brit. J. Radiol.*, 1951, **24**, 507.
[2] Ibid., 1951, **24**, 511.
[3] Philips, F. S., and Thiersch, J. B., *J. Pharmacol.*, 1950, **100**, 398.
[4] Everett, J. L., and Roff, W. C. J., *J. chem. Soc.*, 1949, **3**, 1972.
[5] Goldacre, R. J., Loveless, A., and Ross, W. C. J., *Nature, Lond.*, 1949, **163**, 667.
[6] Paterson, E., and Boland, J., *Brit. J. Cancer*, 1951, **5**, 28.
[7] Karnofsky, D. A., Burchanal, J. H., Armistead, G. C., Southam, C. M., Bornstein, J. L., Craver, L. F., and Rhoads, C. P., *Arch. intern. Med.*, 1951, **87**, 477.
[8] Hansen, P. B., and Bichel, J., *Acta radiol., Stockh.*, 1951, **36**, 469.
[9] Bayrd, E. D., Stickney, J. M., Hall, B. E., and Watkins, C. H., *Cancer*, 1952, **5**, 336.
[10] Silverberg, J. H., and Dameshek, W., *J. Amer. med. Ass.*, 1952, **148**, 1015.

SURGERY ON TELEVISION

An American nation-wide television network on June 10 offered its audience of 30 million viewers a brief relay from the operating theatre of Wesley Memorial Hospital, Chicago.[1] A man of 60 was undergoing a partial gastrectomy, and a close-up view of the surgical field was transmitted as the surgeon continued the operation and explained what he was doing. This is probably the first time that surgery has ever been presented as public entertainment. The relay was sponsored by a Philadelphia pharmaceutical firm in association with the annual meeting of the American Medical Association in Chicago, June 9–13, and was afterwards described as "ill-advised" by the Association's retiring president, Dr. J. W. Cline, according to the *Daily Telegraph's* report.

Operating theatres, unlike courts of law, contain no public galleries and admit no newspaper photographers or reporters. Nor are the patient's relatives and friends invited to watch his operation. This privacy is to spare the patient embarrassment and maintain his right to treatment in secrecy, to spare those near to him unnecessary anxiety, and to spare the surgeon himself the additional worry of a measure of stage-fright, with the possibility of subsequent public criticism of his actions. Even if the coming of television has rendered this old ethical code obsolete, one may wonder where the line will be drawn by commercial sponsors in making matters of life and death into public entertainment. If there is to be any code whatsoever for sponsored television, which we are to have at some future date in this country, relays direct from the operating theatre should be banned as unsuitable entertainment. As for public education, this will be much better served by the showing on television of films specially made to illustrate and drive home such surgical facts as the layman needs to know.

[1] *Daily Telegraph*, June 12.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

CLINICAL EFFECTS OF EXPOSURE TO HEAT AND SUNLIGHT

I. HEAT HYPERPYREXIA AND THERMOGENIC ANHIDROSIS

BY

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Three conditions of clinical importance may result from exposure to heat—namely, heat pyrexia and hyperpyrexia, thermogenic anhidrosis, and heat exhaustion. Exposure to sunlight may give rise to acute sunburn, to hyperpigmentation, or to a variety of chronic intractable skin conditions.

This article deals with heat hyperpyrexia and thermogenic anhidrosis, both conditions in which the basic pathogenic factor is inhibition of sweating. Part II, which will appear next week, will be concerned with heat exhaustion, in which disturbances of both the cardiovascular system and the body electrolyte balance are prominent, and with the clinical effects of sunlight, particularly sunburn.

HEAT PYREXIA AND HYPERPYREXIA

This syndrome covers a wide variety of clinical conditions, ranging from mild fever to hyperpyrexia, and is usually defined as a body temperature of 107° F. (41.7° C.) or higher. The fully developed syndrome of hyperpyrexia is described here; the milder forms of pyrexia call for no special comment. There is a good deal of confusion about this syndrome, owing mainly to the failure to appreciate that it may occur with or without the complicating factors of water and salt deficiency and vascular collapse.

Exposure to heat must continue for some time before the syndrome can develop. Its appearance is not dependent on exposure to direct sunlight. Short bursts of exposure, as, for instance, in stokers, do not usually give rise to serious symptoms. Hyperpyrexia may appear in either sex and at any age; it is commoner in the elderly and unacclimatized. It may occur in indigenous individuals normally exposed to high temperatures.

Predisposing Factors

The evaporation of sweat and the consequent escape of heat may be reduced by excessive or ill-designed clothing, by absence of air movement, or by enclosure in a confined space. The production of sweat may sometimes fall below that required for evaporation, as in extreme dehydration or febrile illnesses, particularly malaria. Overproduction of heat may occasionally be important. Excessive protein intake or overactivity of certain endocrine glands, especially the thyroid, may stimulate metabolism unduly, but the commonest factor involved in excessive heat production is muscular exercise, sometimes initiated or sustained by excitement or overindulgence in alcohol.

A very common predisposing factor is absence or loss of acclimatization to heat. Individuals unaccustomed to hot surroundings are likely to be affected more easily than those acclimatized, but when the latter have lost their acclimatization they become highly susceptible, as do miners when they return to work after a vacation (sometimes after only a few weeks). A history of previous heat intolerance is present in only a small percentage of cases.

Clinical Picture

The onset of acute symptoms may be very rapid, but usually well-defined prodromal symptoms first appear several days before the full syndrome. There is frequently a history of progressive dizziness, sometimes associated with staggering gait, headache, drowsiness, restlessness, and mental confusion. Speaking and swallowing may be difficult and severe and increasing thirst often occurs. When the latter is present and ample fluids are available there may be associated polyuria and frequency. Anorexia, nausea, and vomiting are common in the few days before the onset of fever.

On admission the patient may be in delirium or deep coma. If conscious, he is likely to be restless, anxious, and confused. The oral temperature is very high. In some cases it may be over 110° F. (43.3° C.). The rectal temperature is about 1° F. (0.55° C.) higher. *The skin is dry and flushed.* There may be some cyanosis. The hot dry skin is characteristic of the syndrome and indicates its pathogenesis—namely, complete inhibition of sweating. The breathing is rapid (30 or more respirations a minute) but not panting (the normal reaction to exposure to heat). In coma it may be stertorous or intermittent, or of the Cheyne–Stokes type. The pulse is thin; the rate is fast, often over 130 beats a minute. Occasionally soft systolic murmurs are present, and transient myocardial changes may be recorded in the electrocardiogram. Notable changes in the blood pressure do not occur unless the syndrome is complicated by shock.

The central nervous symptoms are outstanding. In rapidly fatal cases delirium or coma, if present at the outset, is likely to persist to the end. When the illness lasts for some days before a fatal issue early coma may temporarily regress, returning terminally. In most treated cases coma and delirium disappear quickly as the temperature is brought down. Convulsions and muscular twitchings, especially in the limbs, are common. Neurological signs are irregular and vary considerably from patient to patient. They are most severe in patients in whom the effects of the high fever predominate over those of vascular collapse. Their severity is roughly proportional to the temperature.

There are no characteristic changes in either the urinary volume or constituents. If dehydration is present at the time of onset the volume will be reduced and the concentration increased; if salt is deficient it may be absent from the urine. If the patient has suffered from severe thirst and has been drinking freely there may be some polyuria, which may persist for some time after recovery from hyperpyrexia; in these cases the urinary volume is high and the urine dilute, although the total output of electrolytes may be within normal limits. Granular or hyaline casts may also be present in small numbers and there is often some albumin. The blood urea nitrogen is usually a little high—that is, 40–50 mg. per 100 ml. Occasionally, in patients with very high fever, the total blood non-protein nitrogen may rise without a corresponding rise in the urea nitrogen. Total blood and plasma chloride concentrations depend on the prevailing water/electrolyte balance. The concentrations may be within normal limits or may be low when salt deficiency is also present. There is usually a gross reduction in the number of blood platelets and a corresponding increase in clotting and bleeding times.

Without treatment the severe case will progress rapidly to a fatal end. The morbid changes found in the body after death depend largely upon whether the dominant feature was hyperpyrexia or vascular failure. The latter (shock) is a very serious complication. The first effects of shock are reversible, but with the passage of time irreversible and fatal changes occur in the organs, particularly the brain, liver, and kidneys. The development of shock is heralded by remarkable changes in the patient's appearance. The temperature falls rapidly, sometimes to below normal. The flushed dry skin becomes pale, sometimes cyanosed, cold, and moist with sweat. The breathing quickens and becomes

shallower. The systolic blood pressure falls rapidly; the diastolic pressure falls more slowly and may ultimately become unmeasurable. The effective circulating blood volume is greatly reduced and haemoconcentration becomes evident. The patient collapses. If not already comatose he may pass into coma or stupor, or become very restless, irritable, and anxious. Watery diarrhoea is common and there may be incontinence. The urinary volume is reduced and the oliguria may progress to anuria, associated with acute uraemia.

Sometimes evidence of damage to hepatic function is found. The liver edge becomes palpable and tender; epigastric discomfort, nausea, vomiting, and sometimes hiccups develop; some degree of jaundice appears; and bile may be found in the vomit, faeces, and urine. The vascular damage which occurs in shock may become clinically evident. Petechial haemorrhages may appear on the skin and mucous membranes, and the vomit and diarrhoea may contain blood. Pulmonary oedema may dominate the final stages.

In patients in whom there was some disturbance of water/salt balance at the time of the onset of hyperpyrexia, there may be visible signs of dehydration—pinched facies, flabby inelastic skin and tissues, and reduction of chloride in the blood and urine. If vomiting is severe and persistent there may be muscle cramps and sometimes tetany.

Course and Prognosis

If effective treatment is applied early the mortality is low. Death occurs within the first 24 hours in about 70% of fatal cases. It may be delayed for up to 12 days after the onset. Early death results largely from the acute effects of high fever, and later death usually from the effects of complications. The prognosis in an individual case depends to some extent on the length of illness and the height and duration of the fever. The best criterion is, however, the development or otherwise of shock. Shocked patients have less chance of survival. In general, cases with a very acute onset associated with rapidly developing coma are the most likely to die. In practice the overall mortality should be less than 5%.

Diagnosis

There must always be a history of exposure to high environmental temperature for a considerable time. There is usually some history of predisposing causes, particularly ill-advised clothing and heavy exercise. The patient will often volunteer the history of noticeable reduction of sweating, thirst, and polyuria. Diagnosis can be made from the high fever, the flushed dry skin, and the mental condition. *It is essential to exclude other causes of fever, especially falciparum malaria, one of the complications of which is hyperpyrexia clinically indistinguishable from that resulting from exposure to heat.*

Treatment

The high temperature reached in hyperpyrexia is due to failure of sweating. The aim of treatment is to reduce the temperature and promote sweating.

Reduction of temperature is best achieved by evaporation of water from the body surface. The patient should be stripped, covered lightly with a moist sheet, and fanned vigorously, water being applied to the sheet so as to keep up continuous evaporation. The temperature can be reduced by this means much more efficiently and rapidly than by other methods such as sponging with cold water or the application of ice baths. The temperature must be recorded every few minutes. It will begin to fall rapidly after the start of treatment. In the first instance it should not be brought down below 102° F. (38.9° C.), otherwise shock and fatal collapse may ensue. When the temperature has fallen to about this figure active treatment should be temporarily stopped. The temperature usually continues to fall to normal or below after cessation of treatment. Secondary rises are to be expected. If the secondary rise is high, further treatment on the above lines should be instituted. In most cases natural sweating is restored after the first treatment; under these circumstances prognosis is favourable. In very severe cases the return of sweating is delayed and treatment may have to be repeated several times.

The patient should be nursed in as cool a room as can be obtained. Air conditioning is the ideal. He must be kept quiet until well into convalescence.

Unless the case is complicated by water/salt deficiency or vascular failure, no other treatment is necessary. Complications are treated as they arise (see under heat exhaustion in Part II). Sequelae may be resistant to treatment. Mental symptoms require expert handling. Continuous headache may respond to nicotinic acid.

THERMOGENIC ANHIDROSIS

This condition was first clearly defined in the second world war. The syndrome is characterized by some inhibition of sweating, especially on the trunk and limbs, which is, however, never complete, so that high fever does not develop. It is not known whether the inhibition of sweating is central or peripheral. On the whole most authors believe that it is essentially central in origin. It has been pointed out, however, that the high sweat chloride content may be an indication of exhaustion of the sweat glands. There are characterestic skin changes and sometimes enlargement of the axillary and inguinal lymph nodes. The affected skin shows an occluding hyperkeratosis associated with retention of sweat, and ultimately rupture of the ducts of the sweat glands, leading to disorganization of the epithelium and the production of intradermal vesicles. It has been suggested that inhibition of sweating results, at any rate in part, from pathological changes in the local sweat glands. In any given section of the skin, however, relatively few of the glands are affected. Occasionally the skin changes may be observed without the general signs or symptoms. The syndrome may be complicated by water/salt imbalance and cardiovascular disturbances.

Clinical Picture

Thermogenic anhidrosis develops most commonly in individuals who have been exposed to high temperatures for some time. The signs and symptoms are at their worst during the hottest part of the day. Dyspnoea and palpitation are severe after exercise. Increasing periods of rest are required between attempts to work, until finally work becomes impossible. Most patients complain of giddiness, frontal headache, insomnia, anorexia, and epigastric discomfort. There are often subjective feelings of warmth and discomfort, and frequently a tight feeling in the affected skin. The symptoms pass off with rest in cool conditions.

There is nearly always a history of extensive and recurrent prickly heat, which improves and may disappear a week or two before the anhidrosis develops. The patient often notices that in the two or three days preceding the development of the syndrome sweating from the body, but not the face, had progressively diminished. A few days of excessive sweating on the trunk may precede this inhibition.

On examination the patient is restless and apprehensive. His oral temperature ranges from 99 to 102° F. (37.2 to 38.9° C.). The pulse rate is fast, varying from 100 to 130 beats a minute. The respiration rate is increased; rates of over 40 are common. In the uncomplicated syndrome there are no characteristic changes in the cardiovascular system. On the limbs and most of the trunk the skin is warm and dry, except for occasional small islands of sweating. The head and neck, on the other hand, sweat freely, and the palms, soles, axillae, and groin are moist.

The skin changes are characteristic. There are myriads of tightly packed tiny greyish papules about 1 mm. in diameter, many surmounted with vesicles containing clear fluid. Papules occur in patches, especially on the trunk and the upper dorsal aspects of the arms and legs. They commonly develop first on the arms, then on the trunk, and finally on the legs. In some cases the arms, legs, and trunk are

involved simultaneously. The papules do not appear on any moist areas which may be present and are never found on the head and neck. Superficially the skin condition resembles goose flesh, but it is not related to the skin hairs. It may be mistaken for prickly heat, but there is no erythematous ringing of the papules. The skin between the papules is dry and usually warm. Hard oedema of the fingers and arms, associated with enlarged discrete axillary and groin lymph nodes, has been described in some cases.

There are no characteristic changes in the blood or urine except in cases complicated by water/salt imbalance or shock. In some cases in which thirst is a striking feature polyuria may occur, the urine being dilute, with a low chloride concentration; the output of salt in 24 hours is within normal limits. The salt concentration of the sweat is usually high and frequently exceeds 0.5%.

Treatment

Treatment consists chiefly in rest in cool surroundings. Disturbances of water/chloride balance should be controlled by adequate administration of water and salt; parenteral administration is not required in uncomplicated cases.

Treatment brings about a rapid response of temperature, respiration, and pulse. The skin changes disappear more slowly, however, and are often succeeded by branny desquamation which is particularly noticeable on the limbs. Recovery is indicated by increasing ability to exercise without return of symptoms and by the reappearance of sweating, usually first on the trunk. In the early stages of treatment, exertion, exposure to heat, or injection of pilocarpine give rise to a return of symptoms and the peculiar distribution of sweating already described. After recovery, exposure to heat and pilocarpine produce a normal sweating reaction. The enlarged lymph nodes subside after some weeks.

In the uncomplicated case full recovery may be expected in 10 to 14 days. The condition tends to relapse, especially if rest in cool conditions is continued for too short a time. It may be necessary in cases which relapse to remove the patient from the hot environment.

[*Part II will be published in our next issue.*]

APPENDICITIS IN THE WEST INDIES*

BY

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In 1946 I was appointed to the Public Hospital at Georgetown, British Guiana, and in 18 months' work there I was interested to observe that appendicitis was far less common than it is in England. In British Guiana, in a hospital of 600 beds, we removed fewer than 100 appendices each year. However, we noticed from its *Annual Report* that in the Barbados General Hospital of 300 beds about 400 appendicectomies were carried out annually, and we congratulated ourselves on our diagnostic acumen in avoiding unnecessary operations.

On my transfer to Barbados in January, 1948, I was therefore expecting to find appendicectomy being used as a cure-all for a host of conditions. Very soon, however, I found that my expectations were wrong, and indeed since 1948 the number of appendicectomies in Barbados has continued to increase.

In the West Indian Colonies it is possible to discover with reasonable accuracy the incidence of a non-notifiable surgical disease, since almost all operations are done in Government hospitals and the size of the population at risk is known. I have therefore obtained the figures for appendicectomy in most colonies for the 11-year period 1938–48, from their annual medical reports or from the Directors of Medical Services.

In the first Table, the figures relate to the number done each year. In general, few cases of definite appendicitis would be refused operation in these territories, and

TABLE I.—*Appendicitis Rates, 1938–48*

	Average Population	Average Annual Incidence per 100,000	Crude Death Rate per Million Population	Average Case Mortality (%)
Jamaica	1,260,000	200	28	1·4
Barbados	200,000	171	20	1·2
Antigua	40,000	115	21	1·8
Dominica ..	52,000	83	11	1·3
B. Honduras ..	61,000	80	38	4·8
Trinidad	554,000	70 (4 yr.)	19 (4 yr.)	2·7 (4 yr.)
St. Vincent ..	62,000	36	7	2·0
B. Guiana ..	366,000	30	14	4·6
Grenada	85,000	25 (7 yr.)	23 (5 yr.)	9·2 (5 yr.)
St. Lucia ..	74,000	21	7	3·3
Oxfordshire ..		203*		
England and Wales			71·5†	
Italy			39·0†	
Switzerland ..			102·7†	

* Moloney *et al.* (1950). † Young and Russell (1939).

inaccuracies from this cause are not likely to be appreciable. Neither is there likely to be sufficient inaccuracy in the collection of statistics by medical departments to explain the differences. Small differences in the crude death rate should be discounted, but the large ones, as between 28 for Jamaica and 14 for British Guiana, are apparently significant, bearing in mind that the survey covers 11 years.

In most territories the annual incidence shows no definite trend, the figures being roughly constant from year to year in the period of the survey. The figures for Antigua, however, show a marked rise in the last two years of the survey, which has continued in 1949; and those for Barbados show a steady increase in the last five years of the survey, which has continued in 1949 and 1950.

Aetiology

In his monograph on appendicitis, Aschoff (1932) stated that "the frequency of the disease is almost uniform among all peoples of the earth who are under adequate medical and surgical observation." If this is so, can we explain these statistics?

I cannot believe that the professional ability of doctors in these territories varies so tremendously as to account for the observed variations in incidence. The possibility that many appendicectomies in Barbados are unnecessary has been examined by a follow-up (see later).

Different incidences might, however, be due to differences in the standards of hospital service and the availability of medical advice. I have obtained from a well-informed and unbiased source, which must remain anonymous, a classification of the medical services of these colonies into four categories, of excellence or the reverse (Table II).

TABLE II.—*Classification of Medical Services*

Category	Colony	Appendicitis Incidence
A	None	—
B	Barbados	171
	British Guiana	30
	Jamaica	200
	Trinidad	70
C	Antigua	115
	British Honduras	80
	Grenada	25
D	Dominica	83
	St. Lucia	21
	St. Vincent	36

*Read at the Conference of Caribbean Branches of the B.M.A., in Trinidad, January, 1951.

It will be seen that examples of colonies with relatively high incidences and of those with low incidences are found in each group. Aschoff's opinion is therefore not confirmed by these figures. We must seek some other explanation of the variations.

Differences in diet have often been suggested (Short, 1946) as an explanation of the differences in frequency of appendicitis between countries and between different periods in time in one country. Various articles of food have been suggested, on the most tenuous grounds, as being responsible, among them being butter, tea, coffee, cocoa, sugar, rice, bananas, oranges, currants and raisins, iron-ground flour, food preservatives, and meat.

I shall not consider any of these theories except that of meat-eating, which still seems to have some supporters. The diet in all the West Indian territories is low in meat and in all forms of protein. The only available figures (Table III) are those of Platt (1946), and these must be accepted with reserve as there appear to be significant inaccuracies in the basic tables of gross consumption from which his conclusions are derived.

TABLE III.—*Ounces Consumed Per Head Daily, Edible Portion**

	Barbados, 1944	Jamaica, 1942	Trinidad, 1944
Animal products	1·9	1·3	2·6
Starchy roots and fruits Vegetables and fruits	19·7	39·6	13·2
Appendicitis incidence ..	171	200	70

* Platt, B. S. (1946).

Apart from these figures, common sense does not suggest that possible small differences in meat consumption within the West Indies can explain the large variations in the incidence of the disease.

Another popular aetiological theory, supported by Short, is that a low intake of cellulose is related to a high incidence of appendicitis. Table III does not bear out this theory either, and local knowledge suggests that the consumption of cellulose in the different territories does not vary greatly from one colony to another.

Is there a variation in the intrinsic susceptibility of different races? The disease is common in two islands (Jamaica and Barbados) in which the population is predominantly Negro, and relatively rare in two colonies (Trinidad and British Guiana) in which there is a large population of East Indians. In Barbados fewer than 1% of the population are Oriental, and in Jamaica only 2.5% are Oriental. It therefore may be that the Negro is more susceptible than the East Indian. Let us, then, assume that the incidence in Jamaica and Barbados represents the incidence among Negroes and Europeans in the West Indies, and calculate on this basis how many cases we would expect to find among the Negro and European populations of Trinidad and British Guiana (Table IV).

TABLE IV

	Group I: Oriental	Group II: Negro, Coloured, European	Expected Cases Group II Only	Observed Cases in Whole Population
B. Guiana (1944)..	173,700	193,100	376 p.a.	111 p.a.
Trinidad (1946) ..	202,300	355,500	692 ,,	385 ,,

Incidence per 100,000 in Jamaica and Barbados combined = 195.

If the incidence were uniform among the Negro and European populations of the four colonies under consideration the expected cases in this group alone in British Guiana and in Trinidad would be far more numerous than the observed cases in the whole populations of these colonies. Differences in racial susceptibility between Negro and East Indian are not, therefore, the explanation.

Appendicitis in Barbados

Let us now consider in more detail the incidence of appendicectomy in Barbados. Examination of the hospital records shows that there has been a steady rise in incidence between 1920 and 1950, but that the crude death rate from the disease has not altered significantly. This may merely mean an increase in the public's confidence in the surgeon; thus it may reasonably be supposed that the incidence of inguinal hernia is fairly constant from decade to decade and that increased confidence is the reason we now repair more hernias.

In Table V the average incidence of appendicectomy per 100,000 is compared with the average incidence of hernia operations per 100,000. We now repair twice as many

TABLE V.—*Barbados*

	Appendicectomy per 100,000 (Average)	Crude Appendicitis Death Rate per Million (Average)	Hernia Operations per 100,000 (Average)
1919 1920 1921	20	35	34
1929 1930 1931	44	15	60
1939 1940 1941	130	20	81
1948 1949 1950	290	20	78

hernias as in 1920, but remove more than fourteen times the number of appendices.

I have examined in detail the records of all patients submitted to appendicectomy during 1948, and have endeavoured to follow up a random sample of these cases in 1950 to discover what benefit, if any, the operation has conferred. In 1948 (the calendar year) 503 appendicectomies were done, excluding incidental appendicectomies. Of these patients, 116 were male and 387 female. I have arranged them in three groups (Table VI). (I) Gross acute appendicitis, or

TABLE VI.—*Sex and Age Distribution*

	Males	Females	Deaths
I. Gross acute appendicitis ..	36	30	3
II. Subacute appendicitis ..	17	83	0
III. Appendicular pain	63	274	1

Age group ..	0–9	10–19	20–29	30–39	40–49	50–59	60+
Cases	9	193	180	86	21	11	3

cases in which obvious macroscopic inflammation was found and unequivocally recorded, including cases of abscess, perforation, gangrene and peritonitis. (II) Cases in which the clinical picture indicated immediate admission and early operation, but in which the records do not contain clear evidence that gross acute inflammation was found. These I have described as subacute. The fact that case records and operation notes are often lamentably brief makes it probable that some cases of gross acute appendicitis are included in this group. (III) Cases admitted from a waiting-list, presumably suffering from some appendicular disease. This group includes cases of so-called chronic and recurrent appendicitis, but it seems fairer to label them all as "appendicular pain."

The preponderance of cases of mild appendicitis or appendicular pain is obvious, and most of these cases occur in females. The table of age groups indicates that most cases occur in the second and third decades of life. The age and sex distribution again raises the problem whether or not these operations are justified and really represent conscientious and reasonable surgical treatment.

So-called chronic appendicitis has been blamed in the past for a gallimaufry of diseases, including peptic ulcer, gastritis, colitis, cholecystitis, fibrositis, liability to boils, travel sickness, lethargy, anorexia, miscarriages, and headaches. The enthusiastic appendicectomist has sent the appendices he removes to the pathologist, and the pathologists have been

singularly co-operative. Indeed, English (1946) confidently wrote that "all appendices should be examined microscopically after operation. This process *will* [my italics] give convincing evidence of the necessity for the operation." Their evidence, however, becomes less convincing when one discovers that in a series from Detroit (McClure, 1931) of over 1,500 appendices removed during operations on the pelvis or gall-bladder, 95.8% were discovered in the laboratory to be pathological, although presumably few had ever given rise to significant symptoms. This finding is paralleled in several similar series, also quoted by McClure. Nor is the discovery that the appendix is too long or too short, or in the wrong place, or kinked or adherent, or thick or thin, or the home of a faecalith, or even a little injected in itself a justification for operation. If gross acute inflammation is absent, justification for the operation and confirmation of the diagnosis can be found only in the subsequent history of the patient.

My concluding table (VII) summarizes a sample follow-up in 1950 of every sixth case operated on in 1948. Cases have been classified as cured only when there has been no return

TABLE VII.—*Follow-up of Barbados Cases, 1948 (Cases in Sample, 84; Left the Island, 5; Untraced, 7; Followed Up, 72)*

Site of pain:		
R.I.F.	37	72
R.I.F. and umbilical	12	
R.I.F. and right leg	14	
Umbilical or hypogastric	9	
Results:		
Cured	49	72
Relieved	19	
Unimproved	4	

of symptoms similar to those before operation; as relieved when there has been some recurrence of pain (however slight) in the right iliac fossa (R.I.F.) or elsewhere similar to that before the operation, but in which the patient is satisfied with the results of surgery. Other cases are classified as unimproved.

It therefore seems legitimate to conclude that, in Barbados, appendices are being removed for symptoms which suggest appendicitis or appendicular pain, and, furthermore, that the results of appendicectomy are satisfactory even though most cases are not acute.

The anatomist and the physiologist may both interrupt at this point to protest that slight pain in the R.I.F. cannot arise from the appendix, for stimulation of the appendix causes pain felt in the umbilical region. I have attempted to investigate this point by some appendicectomies under local analgesia on patients in Group II and Group III. In the first five patients, stimulation of the appendix invariably caused pain in the umbilicus. In all these cases I had delivered the appendix and caecum through the wound. I then attempted to stimulate the appendix *in situ* in a further eleven cases; in six of these stimulation of the appendix *in situ* caused pain in the R.I.F. even although great care was exercised to avoid stimulation of the parietal peritoneum. In those cases in which exposure of the appendix involved much handling of the intestines or traction on the mesentery, stimulation of the appendix, even if done inside the abdominal cavity, gave rise to umbilical pain. My impression so far is that, if stimulation is heavy or long-continued, pain is felt in the umbilicus, but that if it is slight, and if the appendix is not handled first, pain is felt locally in the R.I.F. I must add that in this investigation analgesia of the parietes must be perfect and the patient must be reasonably intelligent and articulate.

Cases exhibiting definite localized tenderness at McBurney's point—that is, cases in which pressure at McBurney's point causes pain felt beneath the examining fingers—are usually diagnosed as appendicular disease. But in many of these there is no evidence whatever at operation of any inflammation of the parietal peritoneum. The accepted theory of pain in appendicitis is that pain in the R.I.F. is due to inflammation or stimulation of the parietal peritoneum, and that stimulation of the appendix causes umbilical pain. Yet the cardinal sign of appendicitis, without which the diagnosis is made with difficulty and doubt, is pain felt in the R.I.F. on pressure over the base of the appendix.

I have been at some pains to defend the practice of appendicectomy for appendicular pain, for I consider it to be justified in Barbados. I cannot, however, offer any aetiological explanation why mild appendicitis or appendicular pain is common in Barbados and rare in British Guiana. Habitual abuse of purgatives is common in Barbados, but in a small survey of 40 cases of appendicular pain and 44 controls there was no evidence that abuse of purgatives was more marked in one group than in the other.

The present consensus of opinion is that chronic inflammation of the appendix is rare. Yet appendicectomies are done in all parts of the world for recurrent pain in the R.I.F. with tenderness at McBurney's point. To group these cases as appendicular pain does not appear improper, and it avoids the use of a term which carries unjustified pathological implications. Provided that reasonable care is exercised in deciding that the appendix is the source of the patient's symptoms, its removal brings excellent results.

Where appendicitis is common it seems probable that many patients will present themselves for surgical advice and treatment at an early stage of the disease, having suspected that they may have appendicitis and being willing to accept operation if this is advised. Where it is uncommon the patient will not suspect that his bellyache may need an operation, and will tend to persist in home treatment far longer. This may partly account for the higher case mortality in those colonies in which appendicitis is less common.

In this context, both Young and Russell and also Moloney, Russell, and Wilson comment on the relationship in England between social status and mortality from appendicitis. In the Report of the Registrar-General for 1931 the mortality from appendicitis in the highest social group is given as twice that in the lowest. This observation is to some extent confirmed in Barbados by the fact that of 44 deaths from appendicitis between 1938 and 1948, nine cases came from the highest social classes, who certainly make up much less than one-fifth of the population. There seems to be no reasonable medical or surgical explanation for this. One possible relevant factor is that in any country the doctor and the surgeon may be more cautious in advising the admission to hospital of their wealthier and more influential patients, and in doubtful cases admission may be deferred until perforation has occurred.

Summary and Conclusions

The incidence of appendicitis in the West Indian Colonies during the 11-year period 1938–48 has been examined.

Certain large variations are observed, which do not appear to support some current aetiological hypotheses.

When gross acute inflammation is not found at operation it is suggested that the subsequent history of the patient gives a better indication of the value of the operation than is provided by the presence or absence of minor anatomical or histological abnormalities.

My thanks are due to the medical departments of the West Indian Colonies for providing many figures; to Dr. Buchanan, of the Colonial Office; to the D.M.S., Barbados, for permission to publish; and to my colleagues of the Barbados General Hospital for permission to follow up their cases.

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DR. MERVYN GORDON, 80

On June 22 Dr. Mervyn Henry Gordon enters the ranks of distinguished medical octogenarians. For over half a century he has been a familiar figure in the pathological laboratories of St. Bartholomew's Hospital. Gordon displayed a rare originality, being concerned with the beginnings of many branches of microbiological research. With Horder and F. W. Andrewes he helped to distinguish the varieties of streptococci. He was a pioneer of air hygiene, using mouth streptococci as indicators of pollution. But his main interest and claims to fame lie in the field of virus research. He was among the first to transfer mumps virus to an experimental animal, by intracerebral inoculation into monkeys. He developed serological methods for the diagnosis of smallpox, and he made many other contributions to our knowledge of variola and vaccinia. This was at a time when many doubted whether orthodox bacteriological methods could be applied to viruses.

[*Walter Stoneman, London, W.*

During the first world war, when cerebrospinal meningitis was rife, Gordon was appointed consulting bacteriologist to the Army to deal with this problem, and for many years afterwards he continued to serve on the Army Pathological Advisory Committee. Later he embarked on the study of Hodgkin's disease, and discovered that material from affected lymph nodes would cause severe nervous damage when inoculated into rabbits. This—Gordon's test—is an established phenomenon, though most people do not now attribute it, as he did, to the activity of a causative virus. These studies led him in his later years to take a special interest in the possible role of viruses in cancer. Rheumatic fever, measles, and psittacosis were amongst other subjects which engaged his interest and attention.

Mervyn Gordon shunned the limelight, with the consequence that to many bacteriologists Gordon is only a name, but those who have had occasion to consult him retain an enduring impression of his kindness and charm. From them and from many others who have benefited from his life's work best wishes will go out to him on his eightieth birthday.

Nova et Vetera

CROMWELL'S DOCTOR

A Seventeenth Century Doctor and his Patients: John Symcotts, 1592?–1662. By F. N. L. Poynter and W. J. Bishop (Wellcome Historical Medical Library). Publications of the Bedfordshire Historical Record Society, Vol. XXXI. Streatley, near Luton. (Pp. 126. Price: Members £1 1s.; Non-members £1 5s.) 1951.

The history of medicine has been written mainly as that of ideas and of the impact that scientific advances have made on those ideas. It is surprising how little is known of the day-to-day life and practice of medical men of the past. For this reason, if for no other, this account, issuing from the Wellcome Historical Foundation, of a seventeenth-century doctor is specially welcome. Symcotts was not among the "famous men renowned for their knowledge of learning." Rather he was of "those who have become as though they had never been and, though they were merciful men, have no memorial" until this appropriate and pleasant one was raised to him by Messrs. Poynter and Bishop. He was just a normal medical man of the seventeenth century, practising his craft according to his honest but not very exalted best, and just touching history in that, for some years, Cromwell was sometimes his patient.

Symcotts was of Sutton, in Bedfordshire. He was educated at Cambridge, but could have learned little of practical medicine there. Though students were required to attend several dissections, they carried out none themselves. There was no "Physic Garden" attached to the University. The bookwork was altogether mediaeval in character. There was no clinical instruction. We do not know how he learned practical medicine, but he was settled as a physician in Huntingdon before 1628; and his reasonably successful practice extended over Huntingdonshire, Bedfordshire, and Cambridgeshire. There survive from him a case-book and a number of personal documents, all now in the County Record Office at Bedford, a commonplace book of recipes in the library of the Wellcome Historical Medical Museum, and a number of letters in the British Museum. The recipes show something of Symcotts's professional equipment. The admirable marshalling of the whole material gives a revealing survey of medicine as then practised.

Many physicians as the sources of recipes copied are named by Symcotts, but few of them are known to have published anything. It is obvious that their recipes were circulated by correspondence or by word of mouth. They were often copied by Symcotts from the recipe-books kept by both medical practitioners and laymen, but especially by laywomen. Thus Symcotts obtained several recipes from the celebrated Sir Theodore Mayerne (1573–1655), physician to James I and Charles I; the two physicians may have met in consultation, for Mayerne prescribed for Oliver Cromwell. Many remedies Symcotts obtained from ladies, for in his time a lady of good family had to have a practical knowledge of the treatment of everyday ills. Quite a number of their recipe-books survive, one of the most interesting being that of Lady Sedley; some were printed—for example, the Countess of Kent's *Choice Manual*, of which there were 19 editions between 1653 and 1687. Other remedies are attributed by Symcotts to "My sister Symcotts," "My brother Robert," and "My brother Thomas." Symcotts was ready to take recipes from anyone; thus of Mistress Cosens, of Croxton, whom Symcotts attended in 1636 for a purpuric condition during pregnancy: "A beggar woman told her that she would recover if she took shepherd's purse in her broth. Hence I ordered her a broth of plantain, periwinkle, shepherd's purse, etc." Characteristically the regular physician was more willing to take a remedy

from a layman than from a rival practitioner, and he had no good word for the innumerable quacks, empiricks, and itinerant operators.

That Oliver Cromwell was at one time attended by Symcotts was known from a statement in the *Memoirs* of Sir Philip Warwick (1609–83): "After the rendition of Oxford [June, 1646] I was near Huntingdon, and had occasion to converse with Mr. Cromwell's physician, Dr. Simcott, who assured me that for many years his patient was a most splenetic man, and had fancies about the cross in that town, and that he had been called up to him at midnight, and such unseasonable hours, very many times upon a strong fancy, which made him believe he was then dying." The case-book of Sir Theodore Mayerne has a somewhat similar entry for September 15, 1628: "Mons. Cromwell, valde melancholicus." On these points the comments of Cromwell's biographers have varied. Those with the modern "psychological" approach grasp at evidence of abnormality. Stirling Taylor writes that Cromwell "was in the earlier period of his life an exceedingly neurotic person, who sometimes had moods which bordered on instability of mind." One of the latest and most erudite of Cromwell's biographers, Professor Wilbur C. Abbott, says, "Whatever the time and cause, he had apparently gone through that searching religious experience known as 'conversion'; and for various reasons it would appear that it had been caused, or accompanied by, or had resulted in, profound disturbances, emotional and perhaps physical." A further reference to Oliver Cromwell occurs in the Bedford case-book (f. 16a), where Symcotts says that Cromwell, taking mithridate to avoid the plague, found it effective against pimples. There was a close association between Symcotts and other members of the Cromwell family, as Mrs. Baldwin, of Great Staughton, first cousin to Oliver, and Anna Carr, who became the second wife of Henry Cromwell, another cousin.

Symcotts's practice also included humble folk, "the poor woman of Fenton," "Widow King of Godmanchester," and "a little child of John Corbet's," besides the local merchants and shopkeepers who form the staple of a country doctor's practice. Of the latter was Richard Powers, who was, among other things, a coal merchant. A series of letters between Symcotts and Powers illustrate the relations between a country doctor and his patients. Though Powers lived only 10 miles from Huntingdon, correspondence was an accepted and regular means of communication of medical matters. The physician of the day did not feel the need to see his patient often. Diseases were not well differentiated, and there were no exact methods of diagnosis. The present-day doctor thinks nothing of calling on patients within a much wider area, seeing as many in a day as Symcotts in a month, but the seventeenth-century physician did not and could not visit except in desperate cases or when summoned to some patient of high position. Travelling was on horseback, and the state of the roads was such that a 20 miles' journey would be a day's work. A physician would see his patient and outline a general plan of treatment which he would modify from time to time, at need by letter. Such "Consilia"—letters of advice by famous physicians—not infrequently passed from one end of Europe to the other.

Many of Symcotts's cases are of an entertaining kind. We can hardly detail them, but all will wish to read his note on Cromwell:

"De tuberculis rubris faciei" [that is, "pimples on the face"]

"Mr. Ol. Cromwell (long since) taking abundance of Mithridate to avoid the infection of the plague, cured his pimpled face; and this year 1642 Mr. Burrall's eldest daughter, having many small red spots breaking out of her face, was cured principally by the use of mithridate taken every morning, the quantity of about a dram at most at a time."

Two more Symcottian recipes must suffice. These are as good as any:

"How to make the spleen plaster (according to) My lady Pickering

"Take mellilot, camomile, of each three handfuls; parsley, Roman wormwood, plantain, betony, of each of them one handful. Beat them small in a mortar of stone; then put to them three pounds of fine resin, 12 ounces of wax, a pound of sheep's suet, a pint of white wine, and melt all together in an earthen pot. So let them stand seven days; then let them be perfectly boiled and strained and so use it, spread upon a plaster of leather; 'tis good also to be used as salve."

"Ad pulmonum vitia" [that is, "for lung trouble"]

"Take a calf's bladder made clear with bran; put into it of brown sugar candy 1 lb., of pulegii, tussilagiis 1 handful each, anise seeds half a pound, glycyr. rad. 1 handful, and tie up the bladder very close and put it in a skillet of warm water, gently boiling it till it come to a syrup. Strain it through a thin linen cloth and keep it till you have need of it."

Altogether the pamphlet provides an amusing little story, and, by and large, we may say it would serve admirably as a manual of instruction on how not to practise medicine.

CHARLES SINGER.

Preparations and Appliances

OPERATING GLASSES

Dr. GILES ROMANES, clinical assistant, Corneo-plastic Unit, Queen Victoria Hospital, East Grinstead, writes: For many years there has been a large choice of operating glasses, and the simplest types are those incorporating a prism base and a convex lens of low power. This combination overcomes the two major difficulties encountered in doing close work, using binocular vision, by assisting accommodative power and convergence. In addition, some advantage is obtained in the way of magnification by placing the lenses far forward of the eye. All these factors are satisfied by Bishop Harman's operating glasses; some are sacrificed by

Mayou's. The modern surgeon, who uses a face-mask during clinical manœuvres, is unable to avail himself of the benefits of Harman's spectacles and is driven to complex lens combinations.

The operating spectacles illustrated have been developed for use with a mask, and, because of their design, can give magnification, convergence, and accommodation assistance, which is achieved by the extended bridge. The lenses do not foul the mask, nor do they fog with the breath or the wearer's brow sweat. Further, they do not alter their position when the surgeon's head is tilted well forward; and there is adequate room for the use of an ophthalmoscope or similar endoscopic instrument without removing the glasses. These operating spectacles are suggested as being a simple answer to the needs of a surgeon or other worker who is condemned to wear a mask for aseptic reasons. I have had much help from members of the staff of Messrs. C. Davis Keeler, Ltd., from whom the glasses can be obtained.

Correspondence

Prolonged Respiratory Paralysis after Succinylcholine

SIR,—I read with great interest the letter of Dr. J. Kennedy Harper (April 19, p. 866). I feel that the respiratory depression reported by him after the use of 80 mg. of "scoline" was due to overdosage.

We have used succinylcholine prior to endotracheal intubation in 317 cases, and for the maintenance of prolonged muscular relaxation with a continuous intravenous drip in 202 cases. The range of the initial dose of succinylcholine dichloride was from 10 to 30 mg., and the average in the great majority of cases was 20 mg. These doses gave adequate muscular relaxation for three to five minutes in patients anaesthetized with thiopentone (average 550 mg.).

It is known that succinylcholine is hydrolysed by both the plasma cholinesterase and the acetylcholine esterase (F. Bovet-Nitti, *R. C. Ist. sup. Sanità*, 1949, **12**, 138). This hydrolysis is more rapid in man than in cat and dog. In man, in the therapeutic range, the rate of hydrolysis of succinylcholine seems to be independent of its concentration in the organism. However, there is considerable variation in the rate of hydrolysis in different individuals.

If succinylcholine is administered in therapeutic dose, short-lasting muscular relaxation without apnoea can be obtained. When too large a single dose is administered, muscular relaxation will be accompanied by apnoea. The resulting apnoea will last until enough succinylcholine has been hydrolysed to decrease its concentration to the therapeutic level. When succinylcholine is administered in a single intravenous dose, prolongation of muscular relaxation can only be obtained at the expense of apnoea.

Due to the very brief action of therapeutic doses of succinylcholine the prolongation of its action by the repeated intravenous administration of single doses is impractical. Prolonged and readily controllable muscular relaxation can be achieved by the continuous intravenous administration of dilute succinylcholine solutions. Following the initial dose, a 0.16% succinylcholine chloride solution can be administered at the rate of 10 to 60 drops per minute (average 30). This will deliver to the patient about 1 to 5 mg./min., which seems to be the rate range in which succinylcholine is hydrolysed in different individuals. With this method of administration, the intensity of muscular relaxation can be controlled by changing the rate of infusion, and its effects disappear completely within three to five minutes after its administration is discontinued.

We have not yet seen any prolonged respiratory depression after the use of succinylcholine. In contrast, this complication was encountered in 1 to 2% of patients after the use of other muscle relaxants.

Recently, another case of prolonged apnoea was also reported after the use of 100 mg. "scoline" (S. H. S. Love, *Anaesthesia*, 1952, **7**, 113).

It would be deplorable if this excellent muscle relaxant, which provides a greater degree of controllability than almost any agent used in anaesthesiology, should fall into disrepute because of incorrect dosage.—I am, etc.,

Mercy Hospital, Pittsburgh, Pennsylvania. FRANCIS F. FOLDES.

SIR,—I am very pleased indeed to have the opportunity of replying to the letter of Dr. Foldes. The main point raised is the question of overdosage in the case reported by me (April 19, p. 866). I must point out that the dosage used was approximately that suggested by the makers (Allen and Hanburys), and I am sure that anaesthetists in this country are following their suggestions fairly closely.

The great advantage of this drug when used in adequate dose is the complete relaxation so speedily produced, thus obviating haste and trauma in oral intubation. This does not hold good when small doses such as suggested are used. Even more obvious is the absence of "bucking" on introduction of the tracheal tube. The temporary apnoea produced with the dosage I use is an advantage rather than a disadvantage; the few minutes (three to five) of apnoea allows inflation with the maintenance anaesthetic mixture, so bringing the patient under control speedily before "bucking" occurs.

This drug can only satisfactorily be used in maintaining muscular relaxation in prolonged procedures when incorporated in an intravenous drip, when it is a comparatively simple matter to regulate the rate and thus the muscular relaxation. I have used this method experimentally, but for these long operations "tubarine" is my first choice.

The prolonged paralysing effect in the case which I published (recorded also by C. L. Hewer (May 3, p. 971) and by S. H. S. Love) so far has not been explained satisfactorily; it is certainly not due to overdosage. The possibility of a cholinesterase inhibitor—e.g., T.E.P.P.—as suggested by Thesleff (Stockholm) in a personal communication, may well be the explanation. Mention is also made in an article by W. N. Aldridge and D. R. Davies (May 3, p. 945) of the cholinesterase inhibitor effect of "parathion" and "schradan." As these weed-killers and insecticides are now so widely used in agricultural practice, an inquiry into the patient's occupation and the possibility of exposure to one of these substances should be made as part of the pre-anaesthetic examination, if the use of succinylcholine or gallamine triethiodide is contemplated. If in doubt, then a cholinesterase estimation should be carried out.

I have no desire to condemn the use of succinylcholine; on the contrary, I use it extensively and can speak only with enthusiasm of its value in suitable cases. I do, however, feel that it is a mistake to expect a universal application from any one drug. With our present knowledge and wide choice of the relaxant group of drugs it is possible, surely, to pick one suitable to each surgical procedure. The publication of abnormal cases need not necessarily mean that the use of certain drugs should be discontinued, but should stimulate criticism, and help to find out why these abnormalities occur.—I am, etc.,

London, W.1 J. KENNEDY HARPER.

SIR,—A woman aged 55, weighing about 11 stone (70 kg.), with B.P. 160/110, had a high laminectomy (C 1 and 2) for extramedullary tumour. The prone position, head flexed, was necessary. Premedication was "omnopon" ¼ gr. (22 mg.), atropine 1/100 gr. (0.65 mg.), 45 minutes before operation. Induction with thiopentone 0.5 g. was followed by 80 mg. succinylcholine intravenously. She was inflated with oxygen and an orotracheal tube was inserted with ease. Control respiration was carried out with 35% oxygen, gas, "trilene" mixture. The operation was completed satisfactorily after 2½ hours. At the end of the operation respiratory paralysis was still present. Colour was good, eyeballs moist, pulse rate 80 per minute, B.P. 140/80, and nikethamide 5 ml. intramuscularly plus CO_2 was given. Patient was returned to the ward, and O_2 (95%), CO_2 (5%) mixture was administered for five minutes every 30 minutes. During the second and third post-operative days there was still respiratory paralysis. Bronchoscopy was carried out, but no change. "Prostigmin" 1.0 mg., with atropine 1/100 gr. (0.65 mg.), were given intravenously, although prostigmin undoubtedly prolongs the paralysing effect. The patient recovered in about three hours.

I agree with Dr. Kennedy Harper about respiratory paralysis after succinylcholine.—I am, etc.,

Utrecht, Holland. G. GRANT.

Social Trends and Home Confinements

SIR,—I am glad that you gave such prominence to Professor Dugald Baird's criticism (June 7, p. 1246) of my letter on social trends and home confinements, for it is of great medical, social, and economic importance. Without wishing to suggest that he has a narrow outlook I must point out that his letter is based on figures for Aberdeen—which may not be true for the whole country—and that the point of view of his letter is naturally from inside the hospital. Social trends and consequences cover a much wider field, of which G.P.s are perforce acutely aware.

As regards his general criticism, I must reiterate that I postulated a "competent midwife and doctor," for many such can show long series of cases that could compare with most hospital records, and the main purpose of my letter was to suggest that it would, in the long run, be wiser to

spend money and organization to make domiciliary midwifery more competent as well as domestically more convenient than to expand institutional midwifery. I also emphasized the difficulty of introducing the hospital baby into the family, because I realize that a good case can be made out for having the first baby in hospital, where such family difficulties do not arise. I very much doubt, however, whether the case is quite so strong as many of its advocates imagine.

Professor Baird misquotes me when he writes, "Dr. Leak says that domiciliary practice means 'safer midwifery, happier parents, and happier homes.'" What I did write was these ideals "could be secured at less cost" if we made our aim the improvement of domiciliary midwifery instead of, as Dr. Rogers had forecast, almost complete hospitalization. The present cost of maternity beds is already excessive, and in computing man and woman power we have to take into account the vast array of outside ancillary services bringing the patient to hospital and back home again, etc. The question at issue is not what things are but what they might be, and which is the right policy to adopt. Domiciliary midwifery is at least flexible; it takes the service to the patient and does not require any expensive capital outlay or administration.

Professor Baird lays great stress on the reduction of mortality in Aberdeen *pari passu* with the increase of confinements in hospital; but morbidity and mortality in many other directions have also improved during the past 15 years, for which neither hospitals nor health services can convincingly claim credit. The same trend is visible in infantile mortality rates, and local authorities claim much credit in this for the child welfare centres. Without disparaging these any more than I do hospitals, it is an undisputed fact that there are great dangers in bringing many infants together, and that those babies and mothers who would most benefit by the welfare centres are precisely those who keep away from them, because they do not wash or dress their babies well enough for the weekly baby show. Yet they too share in the diminished mortality. Science compels us to acknowledge facts, but popular "social trends" are much pleasanter to follow.

One more point is, I think, worthy of mention and investigation, and that is that I am not alone in having the impression that hospital-born babies are considerably more prone to infection and other upsets for months after they return home than those actually born at home. Hospital services naturally do not see this aspect of their work. Those fortunate enough to see the latest *Glaxo Volume*, No. 6, might find in its article, "Chance, Chickens, and Children," some suggestive thoughts in this connexion, though whether they are truly relevant I cannot say. But I am sure that Professor Baird's kindly criticism by no means disposes of the general thesis of my letter, and perhaps he—or some other expert—would like to tell us whether the "trend" of the past 20 to 30 years of separating mother and baby so early in life has not contributed largely to the disruption of family life which is such a marked feature of our social life to-day. These possible results from undue interference with natural processes may, in the long run, be much more important than a fractional diminution of foetal mortality.—I am, etc.,

Winsford, Cheshire. W. N. LEAK.

SIR,—In the correspondence on the subject of domiciliary midwifery, one person's wishes seem to have been neglected; I refer, of course, to the patient. I believe that most women now prefer to have their babies in hospital (certainly doctors' wives are no exception), for two reasons.

In the first place, many women feel safer in hospital, and Professor Dugald Baird's letter (June 7, p. 1246) gives evidence to justify this feeling.

Secondly, there are numerous social reasons which are underrated or ignored too often by the male mind. For many years there has been full employment, and people able to look after a house while the mother is in bed are almost non-existent, as are also those unmarried sisters who used to help at every domestic crisis, but who now must be self-supporting. The mother feels that she does not wish to become an additional burden to those looking after the family, but prefers to go into hospital, where everything is provided.

So often domiciliary midwifery conjures up the picture of a normal happy primipara, safely delivered of a healthy baby in a pleasant house. Against this should be set a more frequent contrast, in industrial areas, of the dirty house, the low sagging bed in an ill-lit room, with other small children rattling on the door. Is not the answer to this to be found in the general-practitioner maternity home attached to a maternity hospital, where doctors can deliver their cases under good conditions, and fulfil their patients' wish to be delivered in hospital?—I am, etc.,

Hyde, Cheshire. RUTH FITZGERALD.

SIR,—Many of us will agree with much of what Professor Dugald Baird has written (June 7, p. 1246) regarding social trends in present-day midwifery, but the logical conclusion to be drawn from his letter is that if any increase in domiciliary practice would be a retrograde step then an increase in hospital confinement would be progressive. I prefer to think that in Great Britain the balance between hospital practice and domiciliary practice to-day has reached a reasonable level. A further major increase in the number of hospital confinements would require to be followed by a review of our present attitude towards the extended teaching of medical students in midwifery, as proposed by the General Medical Council; by a review of the stated policy of the Royal College of Obstetricians and Gynaecologists on a national maternity service; and by a review of the objects of the newly constituted Midwives' Board.

In the Netherlands the maternal mortality and stillbirth rate was half the Scottish one for many years before we were able to catch up. In that country 80% of the midwifery is domiciliary, and recently they had the lowest stillbirth rate in Europe. I am sure Professor Baird would agree that the present satisfactory maternal mortality rate is due to many factors, and that the introduction of antibiotics, improved medical education, the higher standard of training of midwives, and public realization of the improvement in maternity services and antenatal care have all played a part in achieving this low rate. All would agree that the improved maternity hospital services deserve a share of the credit, but it would be wrong if one did not appreciate that improvements have also taken place in domiciliary midwifery as a result of the same factors, and that still further improvement is possible.

Maternity hospitals are high-cost hospitals, and the fact that many necessarily show an 80% staffed bed occupancy tends to increase the cost to the nation. With the better housing conditions and modern transport, the dangers of domiciliary midwifery in properly selected cases by properly trained doctors tend to be exaggerated. Before accepting Professor Baird's contention *in toto* it would be necessary to examine the position in very much greater detail than is possible in correspondence of this nature.—I am, etc.,

Glasgow. HECTOR R. MACLENNAN.

SIR,—In Professor Dugald Baird's letter (June 7, p. 1246) he states, "Maternal mortality is now one-sixth and stillbirth rate nearly half of what it was 15 years ago, and this great increase in safety has coincided with an increase in hospital confinement."

It has also coincided with the discovery and use of penicillin and sulphonamides, and I am sure nobody will disagree with the suggestion that the latter coincidence is by far the more important factor, and in fact *the* factor in the greatly increased safety in confinements.

With regard to domiciliary confinements, the team-work of the general-practitioner obstetricians and district midwives, working in close harmony, makes for early diagnosis of abnormalities and early hospitalization of those abnormalities requiring hospital

care (only a small percentage of cases). The aid of the "flying squad" for real emergencies has proved a life-saving measure in cases of severe post-partum haemorrhage, and it is rarely necessary for this latter group of cases to be admitted to hospital after the transfusion.

I cannot quote figures for comparison with those of Aberdeen, but I have the feeling that the morbidity figures of these teams would prove to compare favourably with those of the hospitals throughout the country.

It would be helpful if a number of general-practitioner-obstetrician units published their figures for four- or five-year periods—e.g., from 1948 to 1952.—I am, etc.,

London, E.9. ALEC PHILLIPS.

Family Planning

SIR,—Some of your correspondents on this subject have suggested that women go to family planning clinics for unworthy motives. They have suggested, for example, that these women wish to restrict the size of their families, or avoid having children altogether, in order that they may have enough money to buy television sets or other luxuries.

Mr. and Mrs. George Lunn, of the Doncaster Family Planning Association clinic, have recently conducted an inquiry into the reason for attendance at their clinic of 100 women. This is not a large number, but the cases were selected entirely at random and the results are probably representative. They found that these 100 women had already borne 274 children, an average of 2.74 each. This figure is greater than the average number of children per family for the whole nation.

These figures are not presented with any particular pride. We would much prefer women to come to family planning clinics early in their marriages, so that they know how to plan their families and can have the number of children they want and can support. But at least they show that those who say that women come to the clinics for trivial reasons are misinformed.

A fuller report of this investigation will be published in the July issue of *Family Planning*.—I am, etc.,

Family Planning Association, London, S.W.1. DAVID PYKE, Editor, *Family Planning*.

SIR,—It is curious that Dr. Agnes R. S. Sadler (May 24, p. 1132) should regard family planning as a short-term policy. Surely the reverse is the case. Unless we reduce our natural fertility the human race is doomed to starvation, as we are even now reproducing ourselves more rapidly than it is possible to increase our food supply. The only hope is for the white people to perfect methods of birth control and to teach them to the more backward races before famine is upon us all.

The opposition to birth control in this country, which is so impoverished and overcrowded and therefore so helpless, is particularly to be deplored. Let us rather use our ingenuity and common sense to get out of our difficulties. Let us teach our people and also the less-advanced peoples how to stabilize the world population, and keep it at a level which will assure a reasonable standard of living for all. Surely it is better to restrict our population by planning than by war, disease, and famine.—I am, etc.,

Liverpool. RUTH DOVEY.

Diabetes in Infancy

SIR,—The report by Drs. H. S. Brodribb, J. McMurray, and L. G. Scott (May 17, p. 1060) on two young diabetics prompts me to send a few notes on a child of 13 months, now a lad in his teens and on 30 units of Z.P.I. and 20 units of soluble insulin daily. I was called in because the mother thought there must be something wrong with this, her second child. Finding little amiss, but respecting the mother's opinion, I called in on three successive days, and on the third day it was mentioned that the nappies seemed stiffer than usual. That "rang a bell," and the child was admitted to hospital that afternoon, as a specimen of urine had fully reduced Fehling's solution. There is no family history of diabetes. The mother had just got "fed up" with this child, which she could not get off the bottle.—I am, etc.,

Sheffield. G. R. LIPP.

Treatment of Hypertension

SIR,—There is a deplorable neglect of the dietary treatment of hypertension in this country. At a time when the hazards of drug treatment and sympathectomy are still formidable it appears that low-sodium diets should be tried more extensively. Those who have seen how a certain percentage of dangerously ill hypertensives respond to a diet containing not more than 250 mg. sodium (and there is general consensus on the efficacy of this treatment in a good number of cases) must wonder why this comparatively safe method is advocated with so much reluctance and hesitation by the medical profession in this country. While a pilgrimage to the rice fields of North Carolina, which still seems to be fashionable in the U.S.A., strikes one as an overenthusiastic reaction, it is certainly not justifiable to debunk the low-sodium diet because of its insipid taste and the social and personal sacrifices involved. No doctor would hesitate to advocate strict dieting in diabetes or obesity on the grounds that the diet is monotonous and restricted. It would undoubtedly be more constructive if doctors became better acquainted with the compilation of a low-sodium diet (Ucko, H., *British Medical Journal*, 1950, 2, 144) and if attempts were made to help the victims by introducing more fresh and patent sodium-free foodstuffs. There is no salt-free butter in this country, and there are no firms which make bread, biscuits, patent cereals, sweets, chocolate, or any kind of tinned food not containing salt or sodium benzoate. It should also not be difficult to devise artificial sodium-free condiments, but, since the demand for such products is not wide enough, the patient is left high and dry; whereas, if low-sodium diets were prescribed more widely and with less reluctance, this would be a stimulus to the firms concerned to produce suitable sodium-free foodstuffs. This would make the diet more appetizing and also make the patient independent of specially prepared meals at his home.—I am, etc.,

London, W.1. H. UCKO.

Value of Cigarettes after Operation

SIR,—The evils of tobacco have received their due prominence in recent medical literature. The prophylaxis of the "post-operative chest" is at present occupying many minds and hands. A simple remedy—to wit, the use of the post-operative cigarette in the prophylaxis of chest complications—would seem to warrant mention. The elderly sufferer from bronchitis has learnt to "cut his phlegm" with his early morning cigarette. The gratitude of the patient who coughs and splutters up his bronchial secretion with the first puff of a cigarette on the morning after his gastrectomy has convinced even the sceptics of its place in treatment.—I am, etc.,

Nottingham. P. J. BLANEY.

Period of Gestation

SIR,—Mr. A. B. Partridge's statistical treatment (May 31, p. 1192) of unusually long periods of gestation is a misleading over-simplification. It is not generally possible to use a Gaussian distribution curve to predict with certainty the frequency of events which are too rare for observation to give an estimate of their frequency. The Gaussian curve takes no account of large disturbing factors, but only of the combinations of many small factors which give the observed distribution of the bulk of cases. A good agreement with the Gaussian curve shows that large factors are not common, but does not prove that they do not exist. They do occur in many biological systems, and some such factor would seem to have been operating in McKeown and Gibson's Case 1, where the mother repeatedly had long periods of gestation. Again, some overriding limiting factor may come into play at either end of the range of observations. An

obvious example is the impossibility of a gestational period less than zero; yet the Gaussian distribution curve would predict a finite (though extremely small) probability of such an event. This particular limiting factor can often be allowed for by a simple statistical device, and may be dismissed as trivial; but it may well be that, at the other end of the range, new factors come into play to bring pregnancy to an end, quite different from those operating to initiate labour in a normal case.

Factors of both these types may completely alter the frequency of a rare event, without noticeably altering the form of the distribution curve in the region where many observations are available. In fact, we cannot use a well-fitting theoretical curve to state confidently the frequencies of biological events too rare to be collected by observation.—I am, etc.,

Bourn, Cambridge. A. F. PHILLIPS.

Tubo-uterine Implantation

SIR,—Mr. V. B. Green-Armytage (June 7, p. 1222) is to be congratulated on his success in tubo-uterine implantation, and it is timely that the medical world should realize that in the suitably selected case such a procedure has a reasonable chance of success. It would appear that the techniques elaborated individually by Palmer (Paris), Green-Armytage, and myself are similar except for minor details.

Mr. Green-Armytage employs a Silcock punch with which to make a new opening into the cornu of the uterus, a method which is an improvement on that using a fine knife as described by me, because it is easier and a neater opening can be made, although I have not found that stricture has resulted following use of the knife. Of 15 implanted tubes only two have failed to remain open at the uterine end (bilateral patency has not been proved radiographically in the last two cases). Mr. Green-Armytage does not recommend a lipiodologram, and with this I agree, but do not consider that a salpingogram using a water-soluble medium harmful. By means of a radiograph in the follow-up of cases it was manifest that tubal occlusion occurring some months after operation was at the fimbrial extremity in three cases. Since this discovery I have avoided using a probe as guide, or performing intra-abdominal insufflation via the fimbrial aperture, as either of these methods may damage the mucosa. Conception has occurred in three of seven cases of tubal implantation. The eighth case, although possessing tubal patency, was operated on less than a month ago. Pregnancy, as yet, has only been carried to term in one case.

—I am, etc.,

London, W.1. M. MOORE WHITE.

Liverpool Heart Hospital

SIR,—The Liverpool Heart Hospital was founded in 1926. It has done considerable research work. A mansion with extensive grounds had been acquired by the old Heart Hospital committee, 12 miles from Liverpool (Caldy Manor). Its grounds lend themselves ideally for introducing the physical methods of treatment for heart cases and also for rehabilitation. Moreover, it was intended to put the Heart Hospital on a research basis, and adequate laboratory facilities were planned. It was arranged, however, that the out-patient department should remain in Liverpool.

Before the Manor was acquired I communicated with the medical representative of the Ministry of Health, explaining the scheme and pointing out that public funds given specially for the purpose of a heart hospital would be wasted if the Government was not in sympathy with its objects. The Ministry agreed to take over the Manor as a heart hospital, and after examination the Liverpool Heart Hospital also. The old Heart Hospital committee was anxious to do the necessary work of adaptation before nationalization. The estimated cost then was only a few thousand pounds; but there was continual delay in obtaining the necessary permits for the work, and ultimately the Government took over the Manor as it stood. Now, after three and a half years, the scheme has not been completed. Until a few months ago it was the firm resolve of the regional board to make the Manor into a heart hospital, for which it incurred large expenditure, a great deal of which would be absolutely wasted if it were used for any other purpose. Suddenly the board has decided to scrap the whole scheme, and the out-patient department in Liverpool has been closed.

It is interesting to recall that when the Heart Hospital first started in 1926 the general physicians were against its establishment; but under then existing conditions they could not prevent the scheme taking shape. Now, however, under the arrangements prevailing in the National Health Service, the endeavour of a progressive minority is suppressed. Thus progress is impeded and may even become impossible.

It is intended to try to re-establish the Heart Hospital on a voluntary basis.—I am, etc.,

Liverpool. I. HARRIS.

Modified Endotracheal Connector

SIR,—The hooked endotracheal connector here illustrated has been designed primarily for use with oro-tracheal tubes. It is kept in position by hooking the two side-straps of an ordinary Clausen's harness over the hooks, choosing holes which keep the straps just loosely against the neck and cheek. The wide end is connected by a suitable adapter to either a semi-open or closed circuit. The rubber tubing of the adapter takes up a position from the corner of the mouth and across the cheek, just missing the outer canthus of the eye. If necessary the connector can point the other way, leaving the nose, eyes, etc., completely accessible. The third strap of the harness lies free under the patient's head.

The advantages of this simple modification are: it is quite impossible to drag the tube out of the trachea accidentally; it does away with the use of sticky strapping, with all its disadvantages; the hooks can be soldered on to any type of connector. It is essential that the ends of the hooks curve slightly inwards towards each other as shown.—I am, etc.,

London, E.4. G. S. A. KNOWLES.

Work of Health Visitors

SIR,—Your annotation (May 17, p. 1077) focuses attention on the need, beyond dispute, to tidy up much of the socio-medical organization of the National Health Service. To some of us Professor Fraser Brockington's solution is an over-simplification. The duties of health visitor and almoner are different yet complementary; the services of both are essential and need not overlap, provided more than mere lip-service is paid to "co-operation." Can he really assert that infant care and feeding, mental defect in adolescence, and the failing health of a grandparent are "related one to another in such a way that they can rarely be dealt with separately"? Reduplication of health visiting may exist on this alleged scale, but I submit that there is little evidence of it recorded in the *Annual Reports* of medical officers of health of our county boroughs or elsewhere. Will one or more county boroughs not investigate and reveal the real extent among their family units of this reduplication?

My object is to plead for the chest clinic service being allowed to retain its health visitors. In many areas it has been summarily bereft of their services, or the threat of deprivation hangs ominously over it. Since 1948 the best opinion has consistently been in favour of retention of tuberculosis visitors.

It is notable that, in countries where the tuberculosis service has been resuscitated since the second world war or is being built up *de novo*, the basic pattern is retained of the "dispensary" system evolved in Edinburgh by the late Sir R. Philip. Regular home visiting by dispensary nursing staff (and doctors, too) is traditionally part of that system; where visitor and almoner form part of the same team reduplication of visiting need never arise.

Medico-social work in tuberculosis differs from that in other illnesses in several ways. In few others, for instance, is it necessary to visit a family for as long as a minimum period of five, often for 10–20 years. Tuberculosis, as a disease the biggest and by far the most important public health problem of the day, is on the run; we must keep hitting it hard to vanquish it. More of our limited resources, rather than less, need to be directed into the anti-tuberculosis campaign. I fear that the value of tuberculosis visiting would depreciate under the "general purpose" health visitor.—I am, etc.,

Hull. ROBERT HARDY.

Pilonidal Sinus

SIR,—Professor Ian Aird, in reporting a case of pilonidal sinus of the axilla (April 26, p. 902), has furnished one more example of a site in which an acquired and not an embryological origin seems certain for pilonidal sinus. It is interesting to consider the reasons why embryological explanations held the field for so long in the common natal cleft sinuses. Probably the most important was that at the time that surgeons became interested in this condition the climate of surgical thought was so predominantly anatomico-embryological. Moreover, in the spine higher up congenital dermal sinuses, though very rare, were known to occur, often associated with intraspinal dermoids, and various types of teratoma, though rare, were well recognized as occurring in front of the sacrum and coccyx. Professor Aird, however, does not seem sufficiently clear on the aetiology, and to introduce a vague "hormonal or metabolic disturbance which has not been revealed" is merely substituting a more modern shade of mist for the old embryological mists.

The predominant mechanisms of these common conditions seem clear. Almost all are simple acquired infective granulomata. And first of all a word is necessary about the relation of hairs to the origin of the condition. In some sites, as in the digital clefts of barbers, the penetration of the hair is the original cause of the infection. But in other sites this is rare, though I have seen cases of infection of the back of the neck due to tough hairs curling round in their growth and penetrating the adjacent skin. In the post-natal region the commonest mode of commencement is as a chronic infection at the root of a hair or hairs, so that a small pit is produced from the resulting fibrosis. Infection may also occur in a congenital post-anal dimple, or may start as an acne lesion.

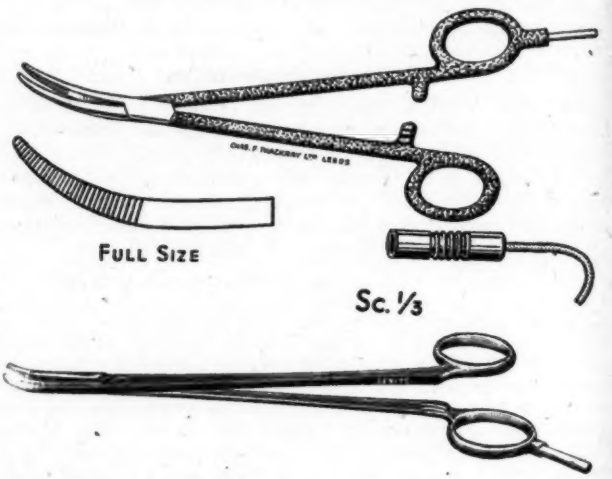
But, whatever the precise original cause of the infection, much more important is the cause of chronicity. And here again a word is necessary about the relation of hairs. Not all these sinuses contain hairs even on microscopical examination. In other words, some of these chronic sinuses are neither pilogenetic nor pilonidal, and yet in site and behaviour are similar to those that are. The explanation, which has only recently been recognized, is that these sinuses persist because they occur in sites—the post-natal region and the clefts in the fingers—where a sucking force is being constantly reproduced. In other words, their essential pathological feature is that they are sucking sinuses. As a result, hairs and other debris on the skin may be sucked in to convert them into foreign body granulomata. A hair foreign body granuloma may be caused other than by a sucking force, and in granuloma of the umbilicus, which is sometimes pilonidal, the mechanism is probably simple accumulation in a depressed pit. But, even without the conversion into a foreign body granuloma, the constant reproduction of a sucking force is a factor in chronicity by counteracting drainage. There are other examples of a sucking force being a potential factor for chronicity, the most striking of course being empyema. I have accumulated but not published some evidence that leads me to believe that this factor may be at work in ischio-rectal abscesses and sinuses, the sucking force being produced by the contraction of the pubo-rectalis muscular sling. And I have speculated that it might be a factor in subphrenic abscess.

Finally, a word on treatment. While, as in Professor Aird's case, excision may be indicated, in the common post-natal site a simple exteriorization operation as discovered empirically by Buie is efficient, and allows healing in a much shorter time. Excision is a theoretical relic of the embryological aetiology of pilonidal sinus, when it was thought that the principle of treatment was wide removal of a possibly complicated developmental track. In fact, excision, owing to the large gap it leaves in the subcutaneous tissue, enhances the sucking mechanism and hence may lead to the recurrence of the sinus if there is any breakdown in healing.—I am, etc.,

London, W.1. DAVID H. PATEY.

Insulated Diathermy Haemostat

SIR,—The instrument described by Mr. Wilson Hey (*British Medical Journal*, 1947, **1**, 897) has been widely copied. The modification illustrated here has the shaft insulated to prevent burning of other tissues by accidental contact. Insulation was originally done for me by T. H. Spicer and Son, 45, Marylebone High Street, W.1, some five years ago, and these forceps have been in use ever since. In the patterns shown here the instrument has been made



longer, being 7 in. (17.8 cm.) in the case of that made by Chas. F. Thackray, Ltd., of Leeds, and 9 in. (22.9 cm.) in that made by the Genito-Urinary Mfg. Co., Ltd., of 28a, Devonshire Street, W.1. The latter is also insulated beyond the joint and is useful in procuring haemostasis after prostatectomy in an obese patient.

I am indebted to the three firms named for their willing co-operation and excellent workmanship.

—I am, etc.,

London, W.1. E. W. RICHES.

Congestive and Simple Glaucoma

SIR,—If a normal disk is defined as one invariably associated with full fields of vision, the statement that glaucomatous field changes can co-exist with a normal disk becomes a contradiction in terms. This definition is implied in Mr. R. Affleck Greeves's letter (May 17, p. 1083).

In my paper on congestive and simple glaucomas (March 1, p. 456), a series of disks was assessed ophthalmoscopically and the results recorded. A later comparison with the findings of an independent examiner of the visual fields proved that some apparently ophthalmoscopically normal disks were associated with glaucomatous field changes. No opportunity was given to the observer of the optic disks to evade a decision. The disks were recorded as pathologically cupped, physiologically cupped (and therefore within normal limits), or not cupped. Such terminology as suspicious or doubtfully cupped disks was avoided.

The apparent difference between Mr. Greeves and myself can be resolved in this way. Those who suspend judgment on a disk until the visual fields are examined will agree with Mr. Greeves; those who make a firm assessment of a disk before examining the visual fields will agree with me that occasionally a disk presumed to be within normal limits ophthalmoscopically will be found in association with the early field changes of glaucoma simplex.

I am glad of this opportunity to congratulate my colleagues on their clinical accuracy, for every case of simple glaucoma discussed in my paper presented some form of cupping and some degree of field defect. In the series of congestive cases, field changes (usually a general depression) were found after an acute or subacute attack, even when the disk was not cupped. It is an old observation that visual acuity can be affected after a

congestive attack without excavation of the disk (Fuchs, *Textbook of Ophthalmology*, 1917, 5th ed., p. 492, London). Further investigation of this aspect of congestive glaucoma is necessary as, so far, it has been largely unexplored.

It was this unexpected finding which led me to state that field changes can co-exist with a normal disk. I made no claim for their being "true glaucomatous field changes," as such a description suggests that they conform to the pathognomonic field loss of glaucoma simplex. There is no evidence for such a supposition and I was surprised to find this phrase attributed to me in Mr. Greeves's letter (April 5, p. 764).—I am, etc.,

London, S.W.1. S. J. H. MILLER.

Balantidiasis in South Persia

SIR,—Dr. A. Geddes McCarey (March 22, p. 629) writes, "The only previous records of balantidiasis in Persia are by Stshensnovitch (1943) and Selimkhanov (1947)." Actually the condition was frequently described by me in the *Annual Medical Reports* of the Anglo-Persian (Anglo-Iranian) Oil Co., Ltd., between 1926 and 1939. These cases were not uncommon in Abadan and occur also in Masjid-i-Suleiman, Ahwaz, Shuster, and many other towns in Khuzistan. As Dr. McCarey states, the infestation is probably transmitted directly from man to man. Dr. McCarey's discovery that acetarsol ("stovarsol") is an effective treatment is a useful advance.

In the *Annual Medical Report* of the Anglo-Persian Oil Co., Ltd., for 1929, three cases of balantidiasis are recorded from Abadan and six from Masjid-i-Suleiman; eight such cases are recorded in 1930; 29 in 1931; two in 1932; 12 in 1934; two in 1935; 47 in 1936; and 37 in 1937, after which the reports were discontinued. Treatment for this condition used to be unsatisfactory; cysts of balantidium were seen in human stools from time to time, but the active vegetative stage was seen most commonly in the dejecta of cases of diarrhoea. Balantidiasis was very rare in Europeans, and was almost confined to the native population of the various centres and towns in Khuzistan.—I am, etc.,

Epping. FRANK MARSH.

Left-sided Appendicitis

SIR,—The literature on transposition of the viscera is a very large one and a considerable number of papers have been published on individual cases. Appendicitis, being such a common condition, must surely have occurred in the past in association with transposition of the viscera, but Mr. W. R. LeFanu, librarian of the Royal College of Surgeons, has been very kind and can find only two previous references to the association of transposition with appendicitis (Bertone, C., *Riv. Chir.*, 1923, **2**, 36; Hollenbach, F., *Dtsch. med. Wschr.*, 1912, **38**, 850). Therefore it is considered worth reporting the following case.

A boy aged 17 was admitted to hospital complaining of pain in the centre of the abdomen. It was not worse on one side any more than on the other. This was followed shortly afterwards by vomiting and then the pain travelled to the left iliac fossa. On examination he was found to be suffering from a dextrocardia, and the liver dullness was present on the left side. There was marked tenderness and guarding in the left iliac fossa present with rebound tenderness. A diagnosis, therefore, of visceral transposition was made associated with acute appendicitis.

Accordingly a McBurney's incision was made on the left side. The caecum was found on the left side; the appendix was in the pelvic position and it presented the usual appearance of acute appendicitis. Appendicectomy was carried out. Abdominal transposition was confirmed; the gall-bladder was palpated on the left side with the normal right lobe of the liver on this side as well. The wound was repaired in the usual way and convalescence was uneventful.

Chest *x*-ray confirmed the presence of dextrocardia, and plain *x*-ray of the abdomen revealed that the stomach shadow was on the right side.

—I am, etc.,

Stourbridge. MAURICE HERSHMAN.

Myositis Ossificans

SIR,—In his illuminating paper Mr. Roy H. Maudsley (May 3, p. 954) states that there is no known treatment. May I suggest the administration of parathyroid in view of the decalcifying action of tumours of this gland? It is probable that the ectopic bone, serving no useful purpose, would dissolve first. Watch on the urinary system would be desirable, since the mobilization of calcium might lead to stone formation.

The term myositis is wrong; the swellings are not limited to bone, they may appear in the skin. Again, no inflammation of muscle produces bone. The condition is one of the blood or blood vessels. The early swellings are haematomas; they are transitory; later the swellings persist, due to calcification, which in its turn gives place to bone according to a fundamental law of bone growth. "Wherever granulation tissues, especially young blood vessels, come into contact with bone or a calcified deposit, bone will form" (A. P. Bertwistle, *The Role of Chemiotaxis in Bone Growth*, 1937, p. 23).—I am, etc.,

Birmingham, 28. A. P. BERTWISTLE.

Value of Organic Manures

SIR,—Having read your leading article (March 22, p. 640) which tells the fascinating story of vitamin B_{12}, so far as it is known at the present time, I feel impelled to write the following comments.

From earliest times husbandmen and other careful observers of Nature have noted and sometimes recorded the effect on the growth of plants of the application of organic manures and composts. The scientific explanation of this phenomenon has become a little clearer with the discovery of vitamins, antibiotics, and plant hormones, as well as of trace elements and other inorganic chemical compounds, and with their isolation from these organic manures and composts and from the fungi, bacteria, and other micro-organisms they contain. Soil microbiology is a relatively neglected study, and the influence of soil micro-organisms on the production and conveyance of the various complex factors concerned with human, animal, and plant nutrition is little understood.

Experiments with plants and animals, especially those of Sir Robert McCarrison, seem to me to show that a greater concentration of vitamins, in particular the B vitamins, exists in grain grown on organically manured soil, and that better nutrition results in rats fed on food so grown.

The interesting story of vitamin B_{12} seems to carry another lesson for us, in addition to those concerning its discovery. It seems to me that the traditional methods of "quality production" of foods should not be lightly thrown aside. The chemical interpretation of plant growth and nutrition which was postulated before the knowledge of the organic and microbiological aspects was understood or much thought of is now seen to be incomplete. Yet much official agricultural policy is still based on these early hypotheses. It is interesting to see how the agriculturists of the U.S.A. have seized upon the new knowledge concerning the growth-promoting properties of aureomycin and other antibiotics and chemotherapeutic substances to bolster up their methods of cheap food production. Surely this cannot be the whole answer to the complex biological process of animal growth and nutrition any more than artificial fertilizers are the answer to the complex biological process of plant growth and nutrition. Neither should we regard the phenomenon of growth as being synonymous with quality in nutrition, any more than we now accept an adequate calorie intake as the only requirement for good nutrition.

We appear to be at the threshold of great discoveries concerning the mechanisms of soil, plant, animal, and human nutrition. All appear to be linked in an ecological balance which may be likened to a cycle of nutrition, the soil, including its teeming micro-organisms, plants, and animals, all being interlinked and interrelated. Man may be regarded either as a parasite or a symbiote in the cycle, who has learned in past centuries to manage part of the cycle to his own advantage. He now dares to interfere to the extent of stimulating his growing crops with certain soluble chemical salts to make them grow and with other more complex chemical substances to stop other plants growing, and in a part-selective manner to prevent the growth of certain insects and micro-organisms regarded as pests. For the future we have the prospect of more antibiotics being sold in the U.S.A. as

growth promoters in food for farm animals than are used in clinical medicine. One wonders if the husbandmen of past centuries were not more wise in their careful non-chemical management of the nutritional cycle, using, however unwittingly, *all* the agents we now have isolated, and others which have not yet been isolated in the perfect ecological harmony we have seen described in our present age among the Hunza tribesmen of North-west India.

The prospect of the ills that may result from the unrestrained use of antibiotics in food to bolster up "cheap production of ham and eggs" is almost as frightening as the physical depredations man has made on the soil of North America and other continents, culminating not only in "cheap" food production, but in "dust bowl" and desert production.

The time has certainly arrived for the physician, the soil microbiologist, the soil scientist, the entomologist, the botanist, the agriculturist, the veterinary physician, and the ecologist to come together in research, but we hope not for the purpose of applying over-energetically the half-knowledge of a complex phenomenon such as growth to produce cheap food.—I am, etc.,

Oxford. ROBERT WIGGLESWORTH.

Plastic Artificial Gullets

SIR,—I was a little discouraged to read the somewhat slighting references in the leading article (May 3, p. 961) to rubber artificial gullets used after excision of the oesophagus. In my last three cases of post-cricoid carcinoma of the oesophagus I excised the growth in one stage by means of a pharyngo-laryngo-oesophagectomy, including the hyoid bone.

The gap between the floor of the mouth and the upper end of the cut oesophagus is bridged by a "portex" plastic tube of approximately 2 cm. diameter. This extends from the level of the base of the tongue superiorly and is inserted inferiorly into the lumen of the oesophagus into which it reaches as far as the mid-thoracic region. Its exposed area is completely covered by a split-thickness skin-graft taken from the thigh and the normal cervical skin flaps replaced and sutured over it. This method seems to have some advantages over that described by Mr. Ronald W. Raven (p. 951). It avoids the distressing intermediary stage of a lateral pharyngostome. Enough of the oesophagus can be removed without anxiety about the practicability of plastic repair afterwards. The oesophagus may be mobilized superiorly, drawn out of the mediastinum, and a reasonable length below the growth excised. After stitching in the tube both are allowed to disappear back into the mediastinum.

I was at first anxious about mediastinal leak, but in none of these cases has it occurred. The nasal feeding tube is removed in two weeks; swallowing by mouth for soft food is then possible, and the patient can leave hospital. The plastic tube is kept in position by a transfixing stainless steel thin wire passed round the neck, and is invisible under a high-necked dress. It is left in position for about two months and then removed through the mouth. I have been able, six months after operation, to pass a child's size Negus oesophagoscope through the new oesophagus, and observe an intact epithelized surface without hair formation and allowing normal swallowing. I owe the first idea of this method to the work of Negus and Robb, which I was privileged to watch in London.—I am, etc.,

Plymouth. D. A. BARLEY.

Incubation of Chicken-pox

SIR,—Dr. G. S. Wolfe (May 10, p. 1030) states that the longest known incubation period for chicken-pox is 23 days. On March 4 in Bombay I saw a child in the scabbing stage of the disease, whom I forbade to travel in the ship of which I am surgeon. I was most dismayed when on March 28 I developed chicken-pox myself (incubation period 24 days). Like the two medical victims who caught the disease in the investigation of a series of herpes zoster varicellosus (March 8, p. 520), I have been in close contact with the disease from childhood onward without contracting it. It seems to be a curious feature of this disease that an apparent immunity possessed by some people is suddenly lost and the disease caught by trivial contact.—I am, etc.,

London, W.2. H. G. DAMANT.

POINTS FROM LETTERS

Ectopia Cordis in Toads

Dr. E. ELKAN (Pinner, Middlesex) writes: The case of ectopia cordis described by Dr. Eleanor J. Wilson (May 31, p. 1175) brings to mind the many cases of an analogous condition seen in Xenopus toads, bred in captivity. . . . Just as in Dr. Wilson's case the heart prolapses through a defect in the anterior chest wall. . . . Not only the sternum but other parts of the skeleton are defective. The young toads so afflicted rarely survive, but one specimen kept under observation has now reached the age of 6 months and shows no signs of dying in spite of a very well developed cardiac hernia.

Chloramphenicol in Reiter's Disease

Dr. JACK CARR (Manchester) writes: It has been suggested that the syndrome known as Reiter's disease is due to a virus. A man aged 30 had a recurrence, in May, 1952, of conjunctivitis, urethritis, and polyarthritis. The symptoms were all severe. Chloramphenicol only was given, in 0.5-g. doses four-hourly for a week. The response to treatment was quick. The conjunctivitis and urethritis had cleared in about five days, and the arthritis was also much improved except for evidence of a small synovial effusion in the left knee. This, however, subsided after a further week. The patient was earlier affected in March, 1951, with the same symptoms. He was treated then in hospital with neoarsphenamine and was symptom-free in a month. The well-marked symptoms and the recurrence would indicate that this was a case of Reiter's disease. The quick and dramatic response this time to treatment with chloramphenicol might suggest that this disease may be virus in origin.

Diffusion Respiration

Dr. M. V. STRUMZA (Paris) writes: I am surprised that our work (see below) has not been noted by your annotator (*Journal*, February 23, p. 430). . . . Our experiments were carried out on more than 200 dogs. Following denitrogenation by pure oxygen, arrest of respiratory movements was effected by several methods: electrical tetanization of the thorax; curarization; deep anaesthesia; section of the medulla; botulinus toxin, etc. We have described a negative intra-tracheal pressure (0.2 to 0.3 ml. water), a lowering of the physiological intrapleural pressure, a rise in the jugular and femoral venous pressure, a lessening of arterial tension, an accumulation of total plasma CO_2, rapid in the first instance then slower, reaching 88.9 volumes % in two hours, a drop in blood *p*H to 6.8 in two hours, a rise in the cell/plasma chlorine ratio of 0.75 in two hours instead of 0.55 (mean), etc. Finally, we showed the role of pulmonary atelectasis at the end of the trial and its harmlessness when spontaneous breathing was re-established. (See *C.R. Acad. Sci. (Paris)*, 1947, **225**, 12; *Rev. Sci. med.*, 1949, **2**, No. 8, 5, 18; *C.R. Soc. Biol. (Paris)*, 1949, **143**, 1413, 1490; ibid., 1950, **144**, 1, 8).

Tale of Three Sneezes

Dr. T. BOWMAN EDGAR (Dumfriesshire) writes: Throughout 40 years of general practice sneezes have not given rise to much serious trouble—perhaps an odd epistaxis here and there, but nothing more—until one Friday morning, around 1.30, when we were called to a coronary patient who was having a very bad attack. She had been awakened by her "husband sneezing in my ear. I thought it was the guns of Korea, and I took a fearful pain in my left arm." That was sneeze Number One. Three days later, at Monday morning surgery, an old patient from the local lodging-house appeared with a dirty scrap of paper in his hand. On it was scrawled, "Doctor I sneezed this morning and haven't been able to speak right since." He had developed a left facial paresis which was later followed by a cerebral haemorrhage from which he died. That was sneeze Number Two. Being superstitious in regard to threes, we were quite sure that we would hear of another sneeze before the next Friday. Sure enough, at 2 a.m. on the Thursday, we were called to a local tradesman who was under observation for a "slipped disk." There was now no doubt whatever of the diagnosis, for he had "sneezed in bed" and made quite sure that his disk was properly, and fully, propulsed this time. That was the third, and last, sneeze of an interesting and unusual series.

Obituary

WILLIAM IBBOTSON, F.R.C.S.Ed.

Mr. William Ibbotson, who died on May 20 in the Royal Northern Hospital, London, at the age of 74, was born on March 18, 1878, and was educated at University College, Sheffield, and at St. Thomas's Hospital, qualifying M.R.C.S., L.R.C.P. in 1903. He was elected F.R.C.S.Ed. in 1923. Before becoming honorary surgeon to the ear, nose, and throat department of the Prince of Wales's General Hospital, Tottenham, in 1923, he held the posts of honorary assistant surgeon at the Metropolitan Ear, Nose, and Throat Hospital, senior clinical assistant to the ear and throat department of St. Thomas's Hospital and the London Hospital, and senior assistant demonstrator in anatomy at the Middlesex Hospital. He was also aural specialist to the Ministry of Pensions and honorary consulting aurist and laryngologist to the War Memorial Hospital, Waltham Abbey, and to Hornsey Central Hospital.

We are indebted to Mr. S. E. Birdsall for the following appreciation: After Ibbotson's retirement from the staff of the Prince of Wales's General Hospital in 1946, he continued for two years at his own wish, so that the work of his department could be kept in order for his successor, who was not released from the Army until 1948. This generous act was characteristic both of his loyalty and of his enthusiasm, which was undimmed at the age of 74, although the last years of his life were spent under the threat of an incurable disease, of which he knew well the nature and prognosis. Ibbotson could look back on an extremely active career. He was mobilized in the Royal Navy on August 4, 1914, and served in H.M.S. *Diamond*, H.M.S. *New Zealand*, the R.N. Hospital, Chatham, and in H.M.S. *Queen* until 1919, later being attached to H.M.S. *St. George* for special service. He was an energetic worker in the field of public health, being aural specialist to the Edmonton education committee. During the last war he was ear, nose, and throat specialist at Rush Green, Waltham Abbey, Queen Mary's at Stratford, and the Royal Waterloo Hospital.

Ibbotson was intensely an individual in his approach to surgical problems. His work was essentially positive and surgical, and his operating and waiting lists were long. If surgical treatment held any prospect of amelioration or of cure, he would always operate rather than temporize. He performed many radical operations on the accessory sinuses, especially the frontal sinus, and he achieved success in many cases in which the conservative school would have hesitated to undertake surgical treatment. In the surgery of the mastoid process he showed understandable uncertainty, his desire to eliminate diseased process conflicting with his desire to conserve the hearing, both being matters of strong principle with Ibbotson. The result was an operation peculiar to him alone, an operation which he called the conservative two-stage mastoid. Although his surgical skill was of a high order he did not attempt the major surgery of cancer, and this was undoubtedly an expression of his faith in the efficacy of physical, especially electrical, therapeutics. For many years he was one of the few advocates of surgical diathermy, especially for tonsillitis. He practised the three-stage destruction of the tonsils by diathermy very extensively at one period, and the fact that he appeared in later years to be abandoning the method may have been due to the increasing skill of his anaesthetists.

Ibbotson's devotion to his patients was a by-word in his main hospital, the Prince of Wales's, and he never lost interest in a case. Consequently his clinics were enormous, and it is often recalled that when he was on holiday an attempt would be made to reduce the size of the sessional gathering by discharging many of the most unpromising types. On Ibbotson's return, however, the old faces would again be seen, awaiting their turn with patient resignation, secure in the knowledge that the surgeon would be the last to leave.

Apart from his professional career, Ibbotson was a man of great culture and of catholic tastes. He was a musician and played the pianoforte with a virtuoso's touch. He could have been a great organist, and his wish was that he could have learned from Buxtehude in the Johanniskirche in Lüneberg, where the young Johann Sebastian Bach sat at the elbow of the master. Although he never published any of his work he wrote many poems, which he circulated among his friends. He was a member of the Poetry Society. It is impossible for one man to be a great surgeon, a great musician, and a great poet, but a man can be surgeon, musician, and poet, and such was William Ibbotson.

Dr. EDWARD CHARLES DUTTON, who died at Stepping Hill, Stockport, on May 18, at the age of 76, was born at Eccles, Lancashire, on January 30, 1876, the elder son of the late Mr. Thomas Dutton, and was educated at Lymm and Hulme grammar schools and at Owens College, Manchester, graduating M.B., Ch.B. from the University of Manchester in 1899. He took the F.R.C.S.Ed. in 1910. After graduation he served with the South African Field Force as a civil surgeon, receiving the medal and five clasps. During the war of 1914–18 he served with the R.A.M.C., with the rank of captain, and was mentioned in dispatches. Dr. Dutton held various posts at hospitals in Liverpool and Manchester, later becoming senior house-surgeon at Stockport Infirmary. He was resident medical officer at Stepping Hill Hospital, Stockport, from 1924 to 1930, and medical superintendent of the hospital from 1930 to 1941. Dr. Dutton, who was unmarried, leaves a brother, who is in Canada, and three sisters in this country. He was greatly loved and esteemed by his patients, colleagues, and members of the staff of Stepping Hill Hospital.

Dr. JOHN PATRICK MORGAN, who died last month, was born in Northern Ireland. He had an interrupted student career at Dublin, for, after two years' study, he joined the Regular Army and served two years in India. On his discharge from the Army he resumed his medical studies, and had just reached his fifth year when war broke out in 1914. He immediately volunteered and served throughout the war. After demobilization in 1918 he again returned to the study of medicine, and qualified L.R.C.P.&S.I. in 1919. Soon after qualification he joined Dr. F. W. Hebblethwaite in practice at Middlesbrough, and they remained in partnership for over 20 years. He then practised alone, until recently he entered into partnership with two other doctors. Of a markedly retiring disposition, to his friends he was generous to a fault and full of charity to his more needy patients; he "clad the naked," sometimes from his own back, and was an example to all practitioners in a working-class practice. No legislation or nationalization, no controls or supervision, not even a sense of duty, can replace the qualities of the natural kindliness of a good heart. It is to the glory of the profession, especially of those in general practice, that such men abound in workaday labour in great content. It is a true vocational spirit that carries them

through all labour and worries. Dr. Morgan leaves a widow and three children. His daughter is married to a doctor, and his younger son, Dr. M. J. Morgan, is at present serving with the R.A.M.C. in India. To his widow and family we offer our deepest sympathy in their loss.—F. J. H.

We learn with regret that Mr. HENRY LAW JACKSON, chairman of H. K. Lewis and Co. Ltd., died on May 29 at the age of 82. Mr. Jackson went to Lewis's as an assistant in 1888; he became a partner in 1905, and was appointed a director in 1915. In 1924 he was appointed chairman, which office he held until his death. Mr. Jackson took a real interest in medicine and the many medical men he met in his long career as a publisher. He regarded the work of his firm very much as a service to medicine and to science, and many were those who profited by his friendly advice and encouragement.

Medical Notes in Parliament

Cremation Bill in Lords

Lord AMMON in the House of Lords on June 10 moved the second reading of the Cremation Bill. He said the Bill, which sought to amend the Act of 1902, had been introduced in the House of Commons as a Private Member's Bill but received the support and blessing of the Government and came before the peers as a recommendation from the whole House of Commons. There were now 60 crematoria in the United Kingdom, and 107,159 people had been cremated in 1951. He assured the House that the safeguards against criminal action were not diminished by the Bill. The Government desired that the Bill should become an Act as soon as possible. The Lord Chancellor commended the Bill to the House and it was read a second time.

Corneal Grafting Bill in Lords

The House of Lords on June 10 went into committee on the Corneal Grafting Bill. Lord LLEWELLIN moved an amendment intended to ensure that bequests of the eyes of deceased persons for therapeutic purposes should be fulfilled whatever form of words was employed.

Lord HADEN-GUEST said he had gone into the matter carefully with the legal advisers of the Ministry of Health and had been convinced that the words of the Bill as they stood would allow the eyes to be used for the good of persons who were blind. He added that the Ministry of Health had taken a considerable part in the drafting of the Bill. Lord Llewellin then withdrew his amendment and the Bill was reported without amendment.

On June 12 the Bill was read a third time in the House of Lords.

Agriculture Bill in Lords

On June 12 in the House of Lords Lord CARRINGTON moved the third reading of the Agriculture (Poisonous Substances) Bill. He said the Zuckerman working party was looking into the possible risk to the health of the public which the use of the poisonous substances covered by the Bill might involve. The working party had completed the sifting of material already available on the question and was now going on to the next stage of hearing oral evidence from organizations concerned.

The Bill was then read a third time.

Facilities for Treating Tropical Diseases in Britain

On June 10 Colonel J. H. HARRISON drew attention to the facilities offered by the Hospital for Tropical Diseases in St. Pancras Way, London, N.W.1. He had tried, but not with much success, to interest the British Medical Association in the improvement of the health of those who had been prisoners of war in the Far East. He asked whether it was not possible for a specialist in tropical diseases periodically to visit provincial centres with publicity beforehand to all local doctors so that they could send him as out-patients men who thought they still had traces of tropical diseases. He asked whether the Government could ensure that the 900 men who were now prisoners in Korea would, on their return, be properly tested to see whether they were suffering from tropical diseases.

Miss P. HORNSBY-SMITH assured Colonel Harrison that the Ministry was ready to do anything possible to bring the facilities of the Hospital for Tropical Diseases to the attention of such persons. The Minister of Pensions was also ready to see that the facilities open to war pensioners were brought to their attention. She said the Ministry had no evidence of unusual prevalence of tropical diseases in this country. It had taken special measures in connexion with malaria, and the Chief Medical Officer of the Ministry of Health shortly after the war had circulated all doctors on the possibility of unrecognized relapses in patients who might have had malaria. A practitioner could refer a patient to the local general hospital, and if it were in the South of England it in turn could send him to the Hospital for Tropical Diseases. It had always been intended that this hospital should be a consultative centre for specialized treatment in tropical diseases, and senior administrative medical officers of the regional boards were well aware of its facilities. It was not easy to send out specialists on tour, but Miss Hornsby-Smith would see whether the regional hospital board in the district for which Colonel Harrison spoke had any evidence of a particular need.

Doctors' Telephones

Mr. IAN HARVEY asked on June 11 to what extent doctors were required to share a telephone line.

Mr. L. D. GAMMANS replied that a doctor was always given exclusive service to his surgery and the line was charged at the business rate. This applied also where his surgery and residence were in the same premises and were served by one line. Since January 1, 1948, all doctors had been under obligation to share their telephone lines to their private houses if they did not practise there. In such cases the line was charged at the residence rate.

Patients' Feeding Costs

Mr. N. N. DODDS on June 12 asked if the detailed investigation had been completed of the proposal of the South-west Metropolitan Regional Board to spend 21s. a week on feeding each patient and a maximum of 14s. a week on each mental patient.

Mr. IAIN MACLEOD said progress had been made in the collection of the necessary data, but the assessment of results would take some time. Comparative costing had been a neglected part of the Health Service and took a long time to be efficient. Preliminary information would be available in a few days. Hospital management committees had been told that if, in certain circumstances, they happened to exceed their estimates this would be allowed.

Mr. A. BLENKINSOP contended that it was wrong for regional hospital boards to attempt to impose maximum costs of this kind. Mr. MACLEOD said the question was not wholly one of economy. Where it was found that a hospital's feeding was below standard the board was taking steps to raise it.

Royal Cancer Hospital

Mr. R. T. PAGET on June 12 asked the Minister of Health whether he would take steps to alter the name of the Royal Cancer Hospital and of any other hospitals under his control whose names had an alarming effect upon the patients. Mr. IAIN MACLEOD said he was prepared to consider any proposal for a change of name put forward by the board of governors of this or any other teaching hospital. Regional hospital boards might, in consultation with the management committees concerned, make such changes in the names of non-teaching hospitals as they thought fit. The board of governors of the Royal Cancer Hospital was considering the matter at the moment.

"National Formulary" and Proprietary Drugs

Mr. HILARY MARQUAND asked Mr. Macleod on June 12, in order to avoid unnecessary expenditure, to advise medical practitioners in the National Health Service, when prescribing proprietary drugs or medicines, to add the letters N.F.E., so that the pharmacist could supply the equivalent according to the *National Formulary*.

Mr. IAIN MACLEOD refused to do this. He said responsibility for specifying the exact substance to be supplied should rest with the prescriber.

Mr. MARQUAND said the suggestion was not his own. The last report of the General Medical Services Committee said it had been turned down because there were legal objections. The Committee appeared to think it a desirable suggestion which would lead to economy. Could not Mr. Macleod remove by legislation the legal obstacles?

Mr. MACLEOD said the proposal had come up many times, but it would have to come from the B.M.A. or the chemists themselves. The chemists felt it would put on their shoulders a responsibility which should not properly be theirs. He did not know the details of the legal difficulties, but understood that the law of copyright affected the substitution of one preparation for another.

Mr. A. C. MANUEL inquired why the Government, which was keen on monetary deterrents for patients, was not prepared to take this step so that medical practitioners prescribed goods which were cheaper but equally good.

Mr. MACLEOD said that, in his view and that of the two professions most concerned, the burden should not be placed on the shoulders of the Ministry of Health.

Mr. F. E. JONES asked Mr. Macleod to consult the Attorney-General about the legal complications.

Mr. MACLEOD said the legal doubts arose over the replacement of a previously named preparation by another.

Mr. SYDNEY SILVERMAN said the problem would be solved if doctors themselves prescribed the *National Formulary* equivalent without the patent medicine.

Mr. MACLEOD said there was a great deal in that remark. He would be glad to follow any avenue which would lead to such an economy.

Mr. ANEURIN BEVAN contended that it would be undesirable for there to be confusion between the general practitioner and the pharmacist as to who should prescribe the *National Formulary*. That might result in greater expenditure.

Mr. MACLEOD agreed.

Drug Prices

Dr. A. D. D. BROUGHTON asked Mr. Macleod on June 12 if he would introduce legislation making it compulsory for pharmaceutical firms to state the prices of their products when advertising drugs and medicines to medical practitioners.

Mr. IAIN MACLEOD agreed that it was desirable that doctors in the Health Service should know these prices, but said he was not clear that the imposing of a requirement to state them in advertisements was a suitable subject for legislation. He would like to think further about the matter.

Dr. BROUGHTON said the medical profession was inundated with literature advertising proprietary preparations and telling the doctor all about them except the price. He said doctors were persuaded to prescribe drugs without knowing the cost which would fall on the National Health Service.

Mr. MACLEOD said he was sympathetic to the idea behind the question. The Ministry had looked into the question of legislation, but there were technical difficulties.

Replying further to Dr. Broughton on June 12, Mr. MACLEOD said no restrictions were placed by his regulations upon medical practitioners in the matter of prescribing drugs and medicines for their patients. If the cost of a doctor's prescribing was found to be more than was reasonably necessary an appropriate sum of money might be withheld from his remuneration.

Dr. BROUGHTON asked for an assurance that Mr. Macleod would instruct executive committees to compare the average cost of each doctor's prescriptions with the average cost over the country as a whole. He asked that the matter would be watched at least as carefully as it had been under the National Health Insurance scheme.

Mr. MACLEOD replied that he had that morning looked at his pricing investigation unit at the Ministry of Health. Dr. Broughton, as a doctor, must know the great difficulty was that pricing was ten months in arrears. The Ministry was trying to get on with the idea Dr. Broughton had in mind.

Rayon Surgical Dressings.—The use of rayon in elastic adhesive dressings, elastic bandages, and cotton crêpe bandages is already authorized. The supply of rayon lint against medical prescription will shortly be approved. Clinical tests of rayon surgical gauze and rayon bandages are still in progress.

N.H.S. Charges.—Estimated savings in a full year from the charges authorized by the National Health Service Acts of 1949, 1951, and 1952 were £12m., £25m., and £7m. respectively, giving a total of £44m.

Medico-Legal

FATAL BREAD CRUST

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

The evidence given on September 3, 1951, before the coroner for the County Borough of Middlesbrough on John Henry Reveley, a 60-year-old steelworker, revealed an unusual train of circumstances leading to his death.

During the last week in June he complained while eating his supper that he had a crusty piece of bread, part of which had stuck in his throat and given him a pain in the chest. On July 23 he saw his doctor about it, and next day he was *x*-rayed. The radiograph showed what appeared to be glands pressing on the oesophagus, so an oesophagoscope was passed, but no damage to the oesophagus could be seen. He was discharged from hospital on August 3. On August 19 he was readmitted to hospital after vomiting blood. He died there on August 25.

Dr. P. N. Coleman, who carried out the necropsy, found a ragged-edged perforation ½ in. (1.3 cm.) in diameter about 4 in. (10 cm.) from the upper end of the oesophagus. This led into an abscess cavity in the mediastinum, which contained altered blood and necrotic material. From the cavity there was a small opening, largely plugged by a blood clot, into the aorta. There was no evidence of aneurysm or of carcinoma or other neoplasm.

Dr. Coleman thought the sequence of events was that a small perforation of the oesophagus at the time of the accident led to infection of the mediastinum and to the formation of the abscess. The original perforation of the oesophagus then probably healed. The mediastinal abscess presently led to a small communication with the aorta, and a leak of blood into the abscess then caused perforation of the abscess into the oesophagus, followed by death. He thought that if Reveley had seen his doctor immediately after the accident the original wound would have been seen; but nothing could have been done and events would have followed the same course.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

Drs. I. W. Broomhead and D. H. M. Woollam have been reappointed University Demonstrators in Anatomy from January 1, 1953, for two years.

In Congregation on June 7 the degree of M.D. was conferred on R. H. Wilkinson and J. O. P. Edgcumbe.

UNIVERSITY OF LONDON

Claud Foster Barwell, M.D., has been appointed to the Goldsmiths' Company's Chair of Bacteriology tenable at the London Hospital Medical College, from October 1.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending May 31 (No. 22) and corresponding week 1951.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire	1952 Eire	1951 Eng. & Wales	1951 Lond.	1951 Scot.	1951 N. Ire	1951 Eire
Diphtheria	24	1	11	1	1	47	5	12	0	2
Dysentery	276	25	84	4	1	753	138	180	4	1
Encephalitis, acute	3	1	0	0		4	0	0	0	1
Enteric fever: Typhoid	3	0	0	0		20	1	0	4	1
Paratyphoid	45	0	12 (B)	0		4	0	3 (B)	0	
Food-poisoning	137	11		3		82	9		0	
Infective enteritis or diarrhoea under 2 years				13	24				13	24
Measles*	6,616	519	376	219	386	15,630	540	500	231	203
Meningococcal infection	31	2	12	3	1	37	2	24	2	1
Ophthalmia neonatorum	39	5	13	0	1	23	0	14	0	
Pneumonia†	380	20	165	7		500	23	163	7	
Poliomyelitis, acute: Paralytic	26	2	2	0	2	16	2	2	1	
Non-paralytic	18	0				12	0			
Puerperal fever‡	225	25	11	1	2	77	9	7	4	
Scarlet fever	915	69	165	16	43	1,043	91	146	31	50
Tuberculosis: Respiratory			175	26				174	43	
Non-respiratory			23	6				29	6	
Whooping-cough	2,595	125	175	81	118	3,218	178	363	94	59

DEATHS in Great Towns	1952 Eng. & Wales	1952 Lond.	1952 Scot.	1952 N. Ire	1952 Eire	1951 Eng. & Wales	1951 Lond.	1951 Scot.	1951 N. Ire	1951 Eire
Diphtheria	0	0		0	0	*0*	0	*0*	0	0
Dysentery	0	0		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0		0		*0*	0	*0*	0	
Infective enteritis or diarrhoea under 2 years	11		4	1	0	*9*		*4*	0	1
Influenza	5	1	3	1	0	*8*	1	*0*	0	0
Measles		0		0	0		0	*1*	0	1
Meningococcal infection		0					0	*2*		
Pneumonia	139	14		9	3	*128*	11		8	6
Poliomyelitis, acute	1	0			0	*0*	0			0
Scarlet fever		0		0	0		0	*0*	0	0
Tuberculosis: Respiratory	87	10	13	2	8	*143*	19	*20*	5	15
Non-respiratory		0	2	1	0		6	*3*	0	3
Whooping-cough	1	0		0	0	*4*	0	*0*	0	0
Deaths 0–1 year	203	21	30	9	13	*211*	29	*26*	11	18
Deaths (excluding stillbirths)	4,479	625	539	98	148	*4,457*	726	*532*	115	175
LIVE BIRTHS	7,758	1149	919	216	427	*7,360*	1218	*955*	219	380
STILLBIRTHS	201	35	21			*190*	35	*21*		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
‡ Includes puerperal pyrexia.

Vital Statistics

Infectious Diseases

The largest variations in the trends of infectious diseases in England and Wales during the week ended May 31 were decreases in the number of notifications of whooping-cough 186 and scarlet fever 55, and a rise of 374 in measles.

The largest increases in the notifications of measles were London 189, Norfolk 111, and Northumberland 105, while the only large decrease was Staffordshire 82. Only small variations occurred in the local returns for scarlet fever. The largest was a decrease of 24 in Lancashire. The largest fluctuation in the number of notifications of whooping-cough was a decrease of 52 in Yorkshire West Riding. The number of notifications of diphtheria was 1 fewer than in the preceding week. The largest variations in the returns of diphtheria were a fall of 3 in Warwickshire and a rise of 3 in Lancashire.

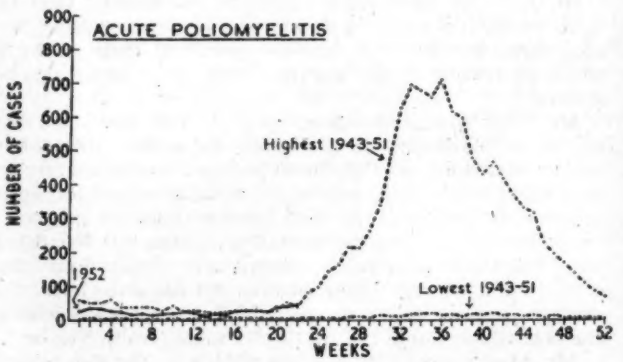
The number of notifications of paratyphoid fever were 8 fewer than in the previous week. Further cases were notified in the outbreaks in Wales, Glamorganshire 17 (Gelligaer U.D. 10), and Monmouthshire 16 (Mynddislwyn U.D. 7).

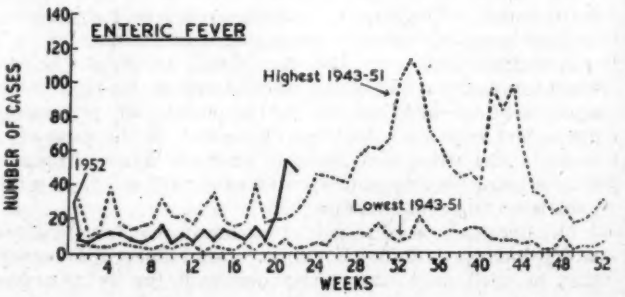
The number of notifications of acute poliomyelitis were 8 more for paralytic and 1 fewer for non-paralytic cases than in the preceding week. The largest centres of infection were Durham 9 (Gateshead C.B. 5), Warwickshire 6 (Coventry C.B. 5), and Middlesex 5.

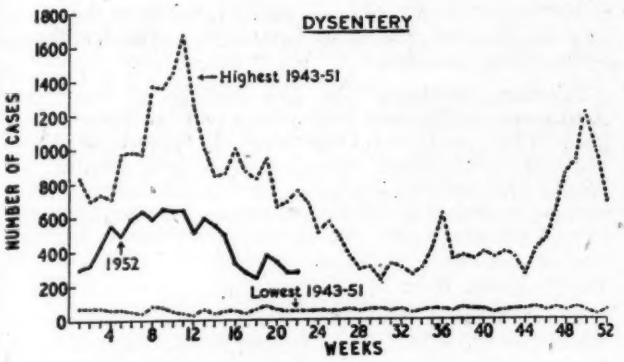
The number of notifications of dysentery were 7 more than in the previous week. The largest returns were Lancashire 88 (Manchester C.B. 38, Bolton C.B. 11, Tottingdon U.D. 10), London 25, Yorkshire West Riding 23 (Batley M.B. 15), Middlesex 22, and Surrey 19 (Wimbledon M.B. 13).

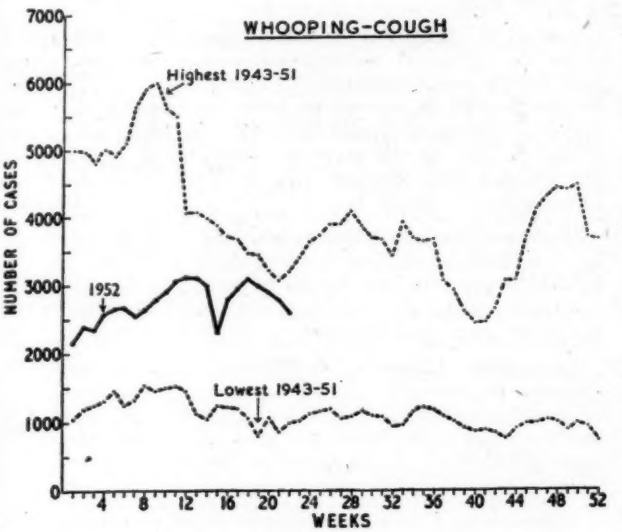
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1943–51 are shown thus -------, the figures for 1952 thus ———. Except for the curves showing notifications in 1952, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Trichiniasis in Barry

We are indebted to Dr. Mary Lennox, medical officer of health, Barry, Glamorgan, for the following information about an outbreak of trichiniasis which occurred in the borough between April 28 and May 4. Over 20 cases have so far been diagnosed—all showing marked eosinophilia. Two biopsies were performed, both showing larvae of *Trichinella spiralis*. Presenting symptoms were headache, facial oedema, and muscle pains, but the majority of patients on close questioning gave a history of gastro-intestinal symptoms during the previous fortnight. All had consumed sausage or sausage meat during the first fortnight in April—with much of it admittedly undercooked. The pork (for manufacturing purposes) which was distributed in the town during the first fortnight in April was not from the usual suppliers in this area, and further investigations are proceeding. It is hoped that a more detailed report will shortly be available. A feature of the outbreak has been the chronicity of symptoms, but fortunately all the patients are now recovering.

Week Ending June 7

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 843, whooping-cough 2,075, diphtheria 29, measles 6,348, acute pneumonia 371, acute poliomyelitis 61, dysentery 210, paratyphoid fever 13, and typhoid fever 5.

Road Accidents in April

During April there were 16,615 casualties on the roads of Great Britain, of which 339 were fatal. Compared with the same month in 1951 pedestrian casualties were 373 fewer this year than last, and the number of pedestrians killed was 22 less.

Medical News

Lady Tata Memorial Trust Awards.—The trustees of the Lady Tata Memorial Fund announce that on the recommendation of the scientific advisory committee in London they have made the following awards for research on leukaemia and other blood diseases, in the academic year beginning on October 1. *Grants for research expenses or for scientific assistance:* Dr. Pascou Atanasiu (Rumania), for work in Paris; Dr. Astrid Fagraeus and Dr. Bo Thorell (Sweden), for work in Stockholm; Dr. Niels Gunnersen Harboe (Denmark), for work in Copenhagen; Dr. Clarence Merskey (South Africa), for work in Capetown; Professor Charles Oberling (France), for work in Paris: Dr. Charles Cady Ungley (Great Britain), for work at Newcastle-upon-Tyne. *Part-time personal grant:* Dr. Jean Baptiste Gabriel Dausset (France), for work in Paris. *Scholarships:* Dr. Jørgen Kieler (Denmark), for work in Aarhus; Dr. Roger Robineaux (France), for work in Paris; Dr. Ragna Rask-Nielsen (Denmark), for work in Copenhagen (half-time). In addition the trustees, on the committee's recommendation, have awarded a senior research fellowship to Dr. A. R. Gopal-Ayengar, chief research cytologist at the Tata Memorial Hospital, Bombay, for work at the Chester Beatty Research Institute of the Royal Cancer Hospital (Institute of Cancer Research, University of London) on the biochemistry of normal and malignant cells.

Hunterian Society.—The annual dinner was held on June 10 at the Savoy Hotel with the president, Sir Arthur Porritt, in the chair. The health of the society was proposed by Lord Woolton, to whose speech reference is made in an annotation on page 1343. In his response Sir Arthur Porritt said that if one-third of the people in this country worked one-third as hard as John Hunter there would be few problems left. Hunter's gospel was the gospel of work. The health of the guests and kindred societies was proposed by Sir Daniel Davies, and replied to by Lord Webb-Johnson and Sir Russell Brain. The Hunterian Prize Medal was presented to Dr. G. M. Temple Tate and a certificate of merit to Dr. M. Solomon (*proxime accessit*). Finally, Sir Arthur Porritt inducted Sir Basil Parsons-Smith as the new president of the society.

Exhibition of Medical Illustration.—The exhibition of photography and art in medicine organized jointly by the medical group of the Royal Photographic Society and the Medical Artists' Association was opened at B.M.A. House on Saturday, June 14, by Sir Harold Gillies, with Mr. H. J. Seddon in the chair. Mr. I. D. Wratten, president of the Royal Photographic Society, and Mr. Gabriel Donald, chairman of the Medical Artists' Association, also spoke, and the general theme of the speeches was that art and photography are complementary techniques, and the practitioners of each should work in friendly harmony. The exhibition itself, though rather specialized, contains some striking work, particularly among the photographs, where the research worker will pick up some useful hints. It remains open till June 28 before moving to the medical school at Manchester, where Sir Geoffrey Jefferson will open it on July 5. Admission is free, from 10 till 5 in London (till 8 on Wednesday), and 10 till 6 in Manchester.

School of Pharmacy.—A Royal Charter of Incorporation has just been granted to the School of Pharmacy by the Queen. From 1842, when the school was founded by the Pharmaceutical Society of Great Britain, until 1949 it was financed entirely by the society. Three years ago, renamed the School of Pharmacy, University of London, it was financed through the University. Now the school is a company limited by guarantee. Medicine is represented on the council of the school by Sir Archibald Gray, Sir Henry Dale, Dr. C. F. Harris, and Professor Buttle.

Study Grants for America.—The American Embassy, the English-speaking Union, and the United States Educational Commission in the United Kingdom announce a programme of grants to assist British graduates to attend universities in the United States of America. The grants will be tenable for the academic year 1953–4.

United States Government Grants: A number of grants in dollars will be available, each including tuition fees for one academic year and a maintenance allowance sufficient for full living expenses. No living allowances are provided for dependants of grantees.

Private Grant Assistance: The Institute of International Education each year assists overseas students to obtain fellowships awarded by American universities. Fellowships from American universities are, however, not always sufficient to cover both fees and full living expenses. Applications will therefore also be considered for a grant to provide dollar assistance to supplement a university fellowship or scholarship.

Candidates who receive assistance in either category may receive a travel grant to cover expenses of travel to and from the United Kingdom and their destination in the United States. No travel expenses will be provided for dependants of grantees. Applicants must be citizens of the United Kingdom or the Colonies, in good health, under 35 years of age, have a bona-fide academic purpose and be prepared to spend one academic year in graduate study at an American university, and hold a bachelor's degree or its equivalent.

Application forms may be obtained from Mrs. D. R. Dalton, B.A., Universities Department, The English-speaking Union, 37, Charles Street, Berkeley Square, London, W.1, after August 1, 1952. Requests for application forms should be accompanied by a short statement containing the following information: name and address (block capitals), field of study, degree (class and university), and present position. All applications must be filed with Mrs. Dalton on or before November 1, 1952. Citizens of the Commonwealth countries should apply to the American Embassy in their own country for information on United States Government Grants and Institute of International Education assistance.

Blood Transfusion Work Award.—The committee of the Oliver Memorial Fund intends making the fifth award of £50 to a British subject whose original work or services in connexion with blood transfusion is considered to be a notable contribution to the research, organization, or donor aspect of this subject. The committee will welcome applications and, in addition, communications drawing their attention to suitable candidates. Applications must be submitted before July 31 next and should be sent to the honorary treasurer, F. W. Mills, Esq., c/o National Provincial Bank Ltd., Holborn Circus, London, E.C.1, to whom all correspondence should be addressed.

New Hospital for Nyasaland.—Construction of a new group hospital in Blantyre, Nyasaland, at a cost of £530,000, is to begin in August. Single-story buildings will at first provide accommodation for 236 beds. In addition, there will be out-patient and casualty accommodation, a central laboratory, and a training school for African hospital assistants. The layout will provide for future expansion by stages, to an eventual maximum of 800 beds.

COMING EVENTS

Child Welfare Conference.—The annual conference of the National Association for Maternity and Child Welfare will be held at Church House, Westminster, S.W.1, June 25, 26, and 27. The general theme of the conference will be "The Wastage of Child Life Before and After Birth." The speakers will include the Minister of Health, Professor Fraser Brockington, Professor T. McKeown, Professor Dugald Baird, Dr. J. Marshall Scott, and Dr. Margaret Hadley Jackson.

International Conference of Geographical Pathology.—The International Society of Geographical Pathology is organizing its fourth international conference, which will take place in Liége (Belgium) on July 15-18, under the chairmanship of Professor J. Firket. The theme will be a study of geographical pathology of hepatitis. The fee is 300 Belgian francs. Details may be had from the secretary, Dr. H. Betz, Institut de Pathologie, 1, rue des Bonnes Villes, Liége (Belgique).

Forensic Pathology.—The fifth meeting of the British Association of Forensic Pathologists will be held on June 28 at 9.30 a.m. in the Department of Forensic Medicine, University of Glasgow, when Professor John Glaister will open a discussion on "Whither Forensic Medicine?" The meeting is limited to fellows, members, and associate members of the association. Those wishing for further information should apply to the secretary, Dr. F. E. Camps, 79, Harley Street, W.1.

Royal Medical Benevolent Fund.—The annual general meeting of the R.M.B.F. will be held on July 24 at 5.30 p.m. at the Medical Society of London. Lord Webb-Johnson will be in the chair.

Course in Industrial Ophthalmology.—A postgraduate course in industrial ophthalmology will be held at the Birmingham and Midland Eye Hospital, July 21 to 25. The fee for the full course will be £4 4s., and remittances, payable to the hospital, should accompany applications. These should be sent to the secretary, Department of Research, Birmingham and Midland Eye Hospital, Church Street, Birmingham, 3, before July 7.

Mackenzie Industrial Health Lecture.—The fourth lecture, on "Medicine and Employment," will be given by Dr. Donald Stewart in the Royal Institution, Colquitt Street, Liverpool, on July 9, at 2.30 p.m. Dr. A. Meiklejohn will be in the chair, and admission is free.

Argentinian Congress of Thoracic Surgery.—The first congress of thoracic surgery under the auspices of the Argentinian Society of Thoracic Surgery will be held in Buenos Aires from September 8 to 12. Details from the general secretary, Dr. Agustin H. Badano, Caseros 2153, Buenos Aires, Republica Argentina.

International Union of Nutritional Sciences.—A European symposium, "Present Problems in Nutritional Research," under the auspices of the International Union of Nutritional Sciences, is to be held at Basle, Switzerland, from October 1 to 4, inclusive. The local organizer is Professor F. Verzár (Physiological Laboratory, The University, Basle, Switzerland), to whom inquiries may be addressed. Fuller information about the International Union of Nutritional Sciences can be obtained from the honorary secretary, Dr. Leslie J. Harris, Dunn Nutritional Laboratory, Milton Road, Cambridge.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, June 23

LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant.—4 p.m., special general meeting of members; 5 p.m., *"Congenital Dislocation of the Hip with Persistent Defect in the Acetabulum,"* by Professor Gunnar Wiberg (Lund).

●POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.—4 p.m., *"The Anterior Pituitary,"* by Dr. Jane Russell (Atlanta, Georgia).

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—5.30 p.m., *"The Surgical Anatomy of the Accessory Sinuses in Relation to the Orbit,"* by Professor T. Nicol.

Wednesday, June 25

RENAL ASSOCIATION.—At Ciba Foundation, 41, Portland Place, London, W., 4.30 p.m., *"The Evolution of Excretory Function,"* by Professor E. Baldwin; *"The Treatment of Nephrotic Oedema,"* by Dr. W. W. Payne.

Thursday, June 26

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—5 p.m., *"The Nature of Congenital Anomalies,"* Ophthalmology Lecture by Professor Arnold Sorsby.

ST. JOHN'S HOSPITAL DERMATOLOGICAL SOCIETY, 5, Lisle Street, Leicester Square, London, W.C.—4.15 p.m., demonstration and discussion of clinical cases.

Friday, June 27

CAMBRIDGE UNIVERSITY.—At Department of Pathology, 5 p.m., *"Recent Developments in the Use of Vaccines Against Infectious Diseases,"* by Dr. Herald R. Cox.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—5.30 p.m., *"Pyococcal Infections,"* clinical demonstration by Dr. S. C. Gold.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, London, W.C.—4.30 p.m., clinical meeting and discussion for general practitioners. *"Stuffy Nose,"* by Dr. H. A. Lucas.

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.—2 p.m., *"Carcinoma of the Rectum,"* by Mr. R. Marnham.

APPOINTMENTS

GAWITH, DONALD H., M.R.C.S., L.R.C.P., D.P.H., Assistant Divisional Medical Officer, Furness Division, Lancashire.

GLENNIE, JAMES S., M.B., Ch.B., F.R.C.S.Ed., Consultant Thoracic Surgeon, Blackpool.

GRIFFIN, JESSIE, M.B., Ch.B., D.P.H., Deputy Medical Officer of Health, County Borough of Eastbourne.

HENSON, R.A., M.D., M.R.C.P., Assistant Consultant Physician, Maida Vale Hospital for Nervous Diseases, London, W.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—*House-physician,* J. H. Diggle, M.B., Ch.B., D.C.H., M.R.C.P. *House-surgeon to Orthopaedic and Plastic Departments,* D. G. Taylor, M.B., B.Ch. *Dental House-surgeon,* R. S. Maclean, M.B., Ch.B., L.D.S. R.C.S.Ed.

HUTCHISON, DOUGLAS, M.B., Ch.B., Medical Officer, Scottish Region, British Railways.

JACKSON, G. A., M.B., Ch.B., D.A.(Part I), Anaesthetic Registrar, South Devon and East Cornwall Hospital, Plymouth, South-western Regional Hospital Board.

LIVERPOOL REGIONAL HOSPITAL BOARD.—*Consultant Obstetrician and Gynaecologist to Hospitals in East and South Liverpool Groups,* Bessie Dodd, M.B., Ch.B., D.P.H., M.R.C.O.G. *Whole-time Consultant Pathologist to Hospitals in Birkenhead Group,* Rachel M. Rawcliffe, M.B., Ch.B. *Whole-time Assistant Psychiatrist to Upton Mental Hospital,* D. P. Hennessy, M.B., B.Ch., D.P.M.

MCCRACKEN, DAVID ANDREW, M.D., D.P.H., Medical Officer of Health and School Medical Officer, County of West Suffolk.

MACLEAN, CHRISTINA I., M.B., Ch.B., Assistant Medical Officer, Maternity and Child Welfare Service, Glasgow.

NORTH-EAST METROPOLITAN REGIONAL HOSPITAL BOARD.—*Full-time Consultant Chest Physician, West Ham Chest Clinic,* D. J. Lawless, M.B., B.Ch., D.P.H. *Part-time Consultant Psychiatrist, Tilbury and Riverside (Orsett Branch) Hospital,* G. S. Prince, M.B., B.Ch., M.R.C.P.I., D.P.M.

ROWLANDS, IRENE PARKER, F.R.F.P.S., M.R.C.P.Ed., Medical Registrar to Herefordshire Group of Hospitals, Birmingham Regional Hospital Board.

TATLOW, W. F. TISSINGTON, M.D., M.R.C.P., Neurologist, Queen Mary Veterans' Hospital and Montreal General Hospital, and Head of Subdepartment of Electroencephalography, Department of Neurology and Neurosurgery, Montreal General Hospital.

WELSH REGIONAL HOSPITAL BOARD.—*Assistant Psychiatrist (S.H.M.O.), St. Cadoc's Hospital, Caerleon,* P. Fry, M.R.C.S., L.R.C.P. *Assistant Traumatic Surgeon (S.H.M.O.), Cardiff Hospital Management Committee,* A. Beck, M.D., F.R.C.S., D.A. *Assistant Medical Officer (S.H.M.O.), Region Blood Transfusion Service, Cardiff,* Beryl Bevan, M.B., B.Ch. *Assistant Radiologist (S.H.M.O.), Caernarvon and Anglesey Hospital Management Committee,* Christine Wowkonowicz, Med.Dipl., D.M.R.D. *Assistant Paediatrician (S.H.M.O.), Pontypridd and Rhondda Hospital Management Committee,* W. Davies, M.R.C.S., L.R.C.P., D.C.H.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Goodman.—On May 6, 1952, to Dr. Ruth (formerly Sabel), wife of Mr. Cyril J. Goodman, 20, Dorset Square, N.W.1, a son.

Gordon.—On June 15, 1952, to Nonette (formerly Harris-Wright), M.B., B.S., wife of Dr. Ian J. Gordon, a son.

Lambert.—On June 6, 1952, to Barbara (formerly Smith), wife of Dr. T. David Lambert, George House, Oxford Drive, Eastcote, Ruislip, Middlesex, a brother for Judith Corinne—Clive Neil.

McGill.—On June 7, 1952, at the Connaught Nursing Home, Cardiff, to Dr. Eileen (formerly Clarke), wife of Dr. A. D. McGill, a son.

Malins.—On June 10, 1952, at the Queen Elizabeth Hospital, Birmingham, to Kathleen, wife of Dr. D. Malins, a son—James William.

Shemilt.—On June 8, 1952, at Salisbury General Hospital, Wiltshire, to Janet (formerly Brownscombe), wife of Philip Shemilt, F.R.C.S., a daughter—Jane.

Twort.—On June 11, 1952, to Frances, wife of Reginald J. Twort, M.D., M.R.C.P., of 6, The Ropewalk, Nottingham, a brother for Alastair.

MARRIAGES

Jackson—Taylor.—On May 2, 1952, at Corbridge, Northumberland, Philip E. Jackson, M.D., M.R.C.P., to Margery Jean Taylor, S.R.N., S.C.M.

Kustow—Justus.—On June 15, 1952, in London, Bernard Kustow, M.B., B.S., to Ann Justus.

DEATHS

Aitken.—On June 13, 1952 at Fairhead Cottage, Grosmont, Yorks, Charles James Hill Aitken, M.D.

Amsler.—On June 11, 1952, at Hawkhurst, Kent, Albert Maurice Amsler, M.B., B.S., formerly of Eton, Bucks, aged 75.

Barratt.—On June 10, 1952, at 193, Leckhampton Road, Cheltenham, Herbert James Barratt, C.I.E., M.R.C.S., L.R.C.P., D.P.H., Colonel, A.M.S., retired, aged 93.

Coalbank.—On June 13, 1952 Robert Malcolm Coalbank, M.R.C.S., L.R.C.P., of 85, Park Road, Teddington, Middlesex.

Tighe.—On June 8, 1952, Charles Tighe, M.B., Ch.B., of Eynsham, Oxford, aged 62.

Veale.—On June 12, 1952, Henry de Paiva Buchanan Veale, M.R.C.S., L.R.C.P., of Clifford House, Ilkley, Yorks.

Versteegh.—On June 7, 1952, at the Gemeente Zickenhuis, The Hague, Arnold Dirk Versteegh, M.D., D.M.R.E.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Hygiene for the Medical Tramp

Q.—*Please suggest some suitable sources of information on hygiene and tropical medicine for a party of medical men planning a walking tour around the Mediterranean. What prophylactic inoculations and insect repellents are advised?*

A.—Two very useful short volumes dealing with these subjects are *Health and Diseases in the Tropics,* by C. Wilcocks (Oxford University Press), and *Memoranda on Diseases in Tropical and Sub-tropical Areas* (H.M. Stationery Office).

Vaccination against smallpox is obligatory, and an international certificate of vaccination should be in the traveller's possession. Inoculation against the enteric group of fevers, though not legally enforced, is advisable.

Di-methyl-phthallate is the most satisfactory insect repellent available. It is marketed in both cream and liquid forms. A few drops of the liquid or a little of the cream should be smeared over the exposed skin, care being taken to avoid the region around the eyes. Plastics are soluble in di-methyl-phthallate; fountain-pens or other objects made from them should not therefore be allowed to come into contact with it.

Mumps Orchitis

Q.—*Where can I find information on the prevention and treatment of mumps orchitis?*

A.—On p. 63 of the book *"Any Questions?"* The book can be obtained for 7s. 6d. (postage 6d.) from the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1.

Dangerous Drugs in the Anaesthetic Room

Q.—*Under Schedule 1 of the Poisons Rules there are some drugs which are commonly used during the administration of anaesthetics. What are the legal and practical requirements for the recording of these drugs?*

A.—If the drugs are to be obtained from the pharmacy for the treatment of an individual patient they must be written on the patient's prescription sheet and signed or initialled by the prescriber. This applies to all poisons, whether Schedule 1 or not. If, however, the drugs are used from "theatre stock" there is no mention in the Poisons Rules of any necessity to record their administration. The Dangerous Drugs Act specifically states that "no record need be kept of a dangerous drug administered by or under the direct supervision and in the presence of a registered medical practitioner or dentist." The Poisons Rules do not make such a statement, but in the absence of any definite ruling or a test case presumably the same procedure would apply.

In practice, however, most hospitals do have a rule that all drugs administered to a patient must be recorded on the prescription sheet or case notes, and it is obviously desirable that this should be done. In many hospitals the theatre sister also keeps a book in which is recorded every dose of D.D.A. drug given and which is signed by the anaesthetist at the end of each case. This prevents D.D.A. drugs from quietly disappearing if there should be an addict around. Such a scheme, however, is not a requirement of the Act. If the anaesthetic were given in a hospital which did not have a pharmacist, then the theatre is not entitled

to keep a stock of poisons and the drugs would need to be ordered beforehand on a medical prescription. In private practice the doctor would use drugs from his own stock; he is not legally obliged to record their administration, but it would be advisable for him to do so in his case notes.

Intradermal Test for Jaundice

Q.—*I understand that a test was used during the epidemics of infective hepatitis among the troops for the early detection of jaundice which involved the raising of an intradermal wheal. Could you let me have details about this test?*

A.—This test was introduced by O. Klein (*Klin. Wschr.*, 1931, **10**, 2032) to facilitate the recognition of jaundice in the pre-icteric stage of infective hepatitis. A bleb is raised on the flexor surface of the forearm by the intradermal injection of 0.2 ml. of a solution of histamine acid phosphate containing 1 mg. per ml. In the normal subject the wheal has a white centre. In the pre-icteric stage of hepatitis the hyperaemic edge of the wheal is yellow within one minute: this is rapidly followed by uniform colouring of the whole wheal. J. D. S. Cameron (*Quart. J. Med.*, 1943, **12**, 139) reported that this test is often positive two to three days before visible icterus is noted.

People on Whom Watches will Not Keep Time

Q.—*Is there anything in the idea that there are some people on whom watches will not go? If so, I am one. Of the many watches I have had, none has ever yet kept decent time.*

A.—Atomic physicists, ophthalmologists, and others who work with large electro-magnets may have trouble with their watches. So may those who combine the frequent use of vibratory weapons, such as motor-bicycles, with an unsuitable clockwork mechanism. Watches removed at night may become inaccurate from temperature differences or because habit places them always in the same position causing selective wear. It is just conceivable that the frequency of the pulse beat in the wrist might synchronize with the hair-spring mechanism and disturb it.

There is no evidence supporting the popular belief that "personal magnetism" or "electricity" may interfere with a watch. Inquiry suggests that this supposed phenomenon is usually supported by second-hand data. Those who make the claim for themselves probably fall into one of the following groups:

(1) Excitable persons who are more violent than they know.

(2) Gullible persons who are poor observers.

(3) Parsimonious persons who buy cheap watches.

Accuracy of Pregnancy Tests

Q.—*What is now accepted as the percentage error with Aschheim-Zondek, Hogben, and Friedman tests, and is it applicable to both positive and negative findings?*

A.—The percentage error with the Aschheim-Zondek and Hogben tests has been reported on by Landgrebe and Hobson (*British Medical Journal*, 1949, **2**, 17). They found that with the former test 99% accuracy was obtained in 12,567 cases in their own laboratory, there being doubtful results in 0.18%. False negative results occurred in 0.72% and false positive in 0.08% of cases. From a study of the literature they found a mean figure of 97.9% accuracy in 26,163 cases reported by 43 authors and 97.2% accuracy in a further series of 5,455 cases reported by 13 authors; in this latter series the false negatives constituted 0.72% and the false positives 1.2% of cases. With the Hogben test, their own figures were 99.65% accuracy in 5,666 cases, with no doubtful results, 0.32% false negatives, and 0.03% false positives. These figures were compared with 98.9% accuracy for 7,707 cases reported by 14 other authors, the false negatives being 1.1% in this series and the false positives non-existent. Comparable figures, based on so many cases, do not appear to exist for the Friedman test, but an accuracy of about 98% has been accepted by most workers, again with a slight excess of false negatives over false positives. It should be emphasized that with all pregnancy diagnosis tests scrupulous attention to technical details is essential if the high degree of accuracy mentioned above is to be obtained.

Syncope and Fatal Wasp Stings

Q.—*At a recent inquest on a woman who died after a wasp sting the cause of death was declared to be "syncope." What precisely does this term mean, and is it properly used in the example cited?*

A.—Syncope is defined as "fainting" and is attributed to cerebral anaemia. In medical jurisprudence, however, it has assumed the meaning of a "sudden cessation of the action of the heart," and hence a sudden death due to cardiac arrest such as occurs in vagal inhibition. Although it is possible for a wasp sting, under the correct conditions of surprise or hypersensitivity and acting as a painful stimulus, to cause vagal inhibition, death from such stings is usually due to an acute allergic reaction. This, although rapid, is not instantaneous and is usually accompanied by some oedema of the glottis and bronchospasm. There appears to be an individual idiosyncrasy in fatal cases, and most single fatal stings are situated on a mucosal surface such as the lip or tongue.

Stains from Medicinal Dyes

Q.—*Is there any way of removing the stain left by a mixture of gentian violet, brilliant green, and spirit, used for the treatment of paronychia? The stain persists until the nail has grown out.*

A.—The stain should be treated with a solution of sodium hypochlorite, such as "eusol," Dakin's solution, or one of the proprietary hypochlorite bleaches, which should be allowed to act for several minutes. A dilute solution of hydrochloric acid should then be applied for a few minutes followed by thorough washing. If the stain is very dense several treatments may be necessary.

Recurrent Iritis

Q.—*What are the likely causes and treatment of recurrent unilateral iritis in a man of 30? He has had 14 attacks, each lasting two or three weeks, in as many years.*

A.—The usual causes of iritis should be eliminated: they include endogenous infection from a septic focus in the teeth, tonsils, sinuses, etc., syphilis, gonorrhoea, and tuberculosis. The history of this case is very suggestive of gonorrhoeal infection, such cases often requiring prostatic massage. Atropine should be used locally in 1% strength, either as drops or as an ointment.

NOTES AND COMMENTS

Correction.—In the Refresher Course article, "Fractures in the Aged" (June 7, p. 1240), it was stated that dienoestrol was "similar to stilboestrol but stronger." This is incorrect: stilboestrol is about four times as powerful as dienoestrol (see *National Formulary 1952*, p. 27).

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